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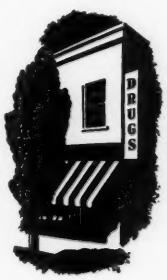

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REPLACEMENT OF THE FEMORAL HEAD IN SEVERE OSTEOARTHRITIS OF THE HIP*

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BOSTON

THE pain and disability in severe osteoarthritis of the hip joint are often not relieved by conservative measures.[1] In these severely damaged joints surgical procedures have been employed with increasing frequency. The surgical measures can be divided into five types: operations to improve the circulation[2] in the femoral head and neck,[3] operations to denervate the articular capsule of the hip joint,[4] operations to stop all motion[5] at the hip joint,[6] operations to change the line of weight bearing coming through the hip joint[7] and operations to improve motion by removing the bony proliferation[8] about the femoral head and acetabulum, at times combined with arthroplasty.[9] Of these measures three are frequently employed at present: obturator neurectomy, arthrodesis and cheilotomy combined[9] with arthroplasty.[10, 11]

Each of these procedures attempts to correct one or more of the anatomic and physiologic disturbances found in osteoarthritis but fails to correct satisfactorily the faulty mechanics of the hip joint. Obturator neurectomy combined with denervation of the posterior capsule is a helpful palliative procedure for lessening pain in elderly patients. Arthrodesis[12] of the hip joint relieves pain but leaves a stiff hip[13] to which the older patient has difficulty in adjusting himself.[14] The conventional type of arthroplasty, although it improves motion, usually does not correct the mechanical faults of the hip joint.[15]

TABLE 1. *Criteria for Grading Function of the Hip.*

GRADE	PAIN	MOBILITY	AMBULATION
0	Constant, severe	Ankylosis or severe deformity	Patient unable to walk
1	Severe, even at night	No movement without pain; moderate deformity.	Only with crutches
2	Severe when patient is walking, preventing any activity	Flexion under 40°	With 2 canes
3	Moderate with limited activity	Maximum flexion between 40 and 60°	With 1 cane less than 1 hr.; difficult without cane.
4	Mild when patient is walking, disappearing with rest	Maximum flexion between 60 and 80°; patient can reach foot.	Walking for a long time with cane; little without cane but with limp.
5	Mild and inconstant, permitting normal activity	Maximum flexion between 80 and 90°; abduction at least 15°.	Without cane but with slight limp.
6	Absent	Maximum flexion more than 90°; abduction to 30°.	Normal

In severe osteoarthritis there is extensive deformation of the femoral head, usually combined with varus and torsion of the femoral neck.[16] Unless these are corrected, the faulty mechanical use of the hip will lead to a continuance of symptoms and further bony proliferation.[17] To obtain good mechanical use of the hip joint, the deformed head should be reshaped or replaced, the twisted femoral neck corrected, and the acetabulum made adequate and aligned to the femoral head and neck. These mechanical faults can be corrected most easily and effectively by replacement of the distorted femoral head with a prosthesis.

At first, attempts were made to overcome these deformities by metallic replacement of the entire femoral head and neck.[18] The wide exposure necessary for the attachment of the prosthesis and the large amount of metal exposed led to rather exten-

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sive fibroses and calcification about the articular capsule. This suggested the use of smaller amounts of exposed foreign material and a less extensive operative exposure, important factors in elderly patients. The posterolateral incision described by Gibson[19] was found to be the most satisfactory, providing good visualization of the acetabulum and the entire femoral head and neck (Fig. 1).

In the first two years of this work the prosthesis employed was molded of methyl macryalate[20] and

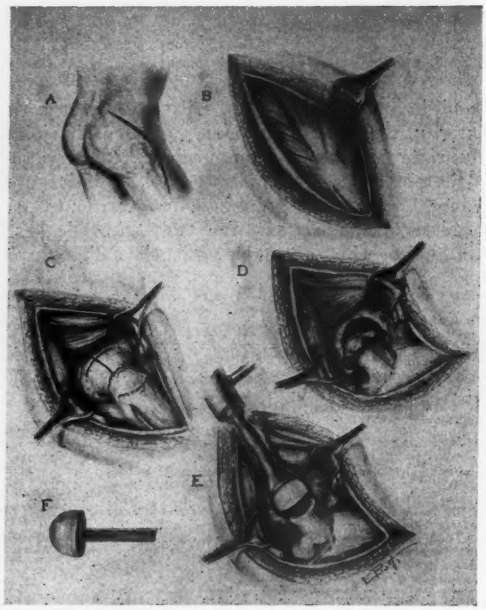


FIGURE 1. *Procedure for Removal of the Femoral Head and Insertion of Prosthesis.*

A = *posterolateral incision.*

B = *incision of fascia.*

C = *removal of insertions of gluteus medius and minimus muscles and a portion of gluteus maximus muscle from the greater trochanter.*

D = *dislocation of the deformed femoral head from the acetabulum.*

E = *insertion of prosthesis after proper angulation of femoral neck.*

F = *prosthesis with attached nail.*

fitted to a triflanged nail by a local dental laboratory (Fig. 1*F*). This ensured both an inexpensive appliance and one of the proper size required in each operation. From a study of the x-ray picture of the diseased hip, the size of the plastic head and the length of the attached nail were determined. However, it was found advisable to have several sizes available when extreme deformity was present. Since the prosthesis was not visible in the x-ray picture, 3 per cent barium sulfate was mixed with the plastic. During this period many prostheses both of metal and of plastic were produced by manufacturers of surgical appliances. These prostheses were as satisfactory as the original ones. No difference was observed in the wearing qualities or in the reaction of the tissues between the plastic and the metallic prostheses.

In the replacement of the deformed femoral head after reflection of the fascia, section of the insertions of the gluteus medius and minimus muscles and dislocation of the hip joint, three procedures were employed in varying degree to correct the mechanical faults (Fig. 1). In the first place the angulation of the femoral neck and the amount of anteversion or retroversion were determined; the femoral neck was then sectioned with a saw in a manner to correct the directional slant of the femoral neck or to make it similar to the more nearly normal opposite side. Secondly, the bony overgrowth about the acetabulum was removed, and the acetabulum was deepened or realigned with the femoral head and neck. Finally, the nail of the prosthesis was driven through the cross-section of the femoral neck into the firm cortical bone below the greater trochanter. The articular capsule and gluteal muscles were resutured, the wound closed, and a plaster boot that held the leg in internal rotation was applied.

TABLE 2. *Results of 42 Operations.*

CONDITION	NO. OF PATIENTS	FINDING
Very good	4	No pain; no limp; normal motion.
Good	28	No pain; slight limp; patient uses cane; motion 60°–80°.
Fair	7	Slight pain when patient is tired; patient uses cane or crutch; 40°–60° motion.
Poor	3	Pain on walking; motion less than 40°; patient uses 2 crutches or 2 canes.

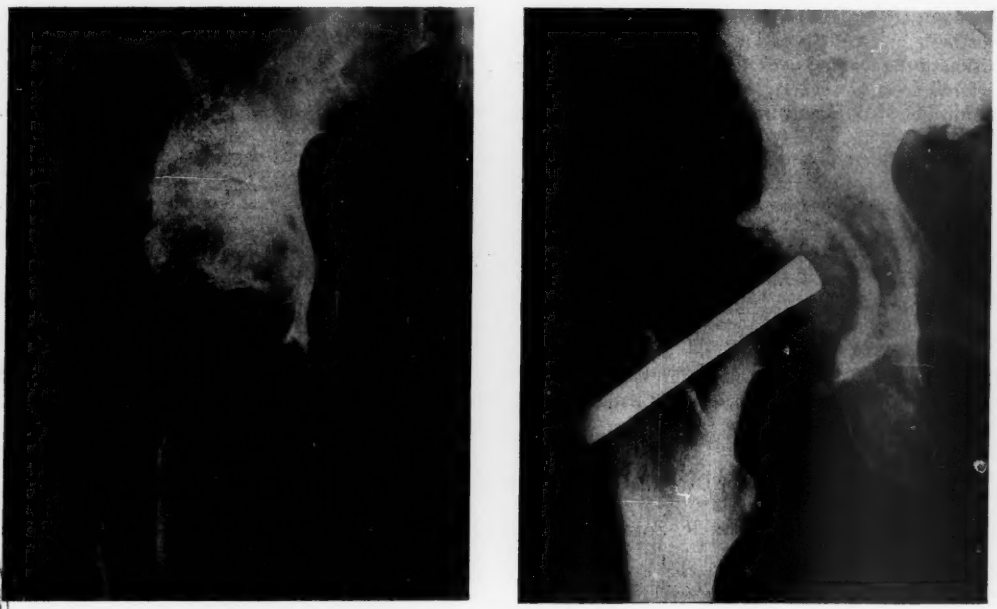
TABLE 3. *Complications.*

TYPE	NO. OF CASES
Subluxation of hip	5
Postoperative migration of nail	2
Separation of sutured muscles	1
Breaking of nail	1

It was found advantageous to begin motion early in these elderly patients.[21] Muscle-setting exercises were begun in a week. These were followed by active nonweight-bearing exercises. Walking in a walker was permitted in three weeks unless extensive bony atrophy was present. Resistance exercises were begun after a month. Recovery of strength in the gluteal muscles required about six months. Usually at this time the patient could walk without support.[22]

This operation has been performed in the treatment of 42 severely deformed osteoarthritic hips.

The typical x-ray appearance before and after correction is presented in Figure 2. In all cases function has improved. Pain has been lessened or has been entirely removed. The most satisfactory criteria for grading the functional efficiency of the hip joint are found in the tables of Judet[23] and of D'Aubigné.[24] These criteria are summarized in Table 1. Originally, the hip joints were graded 0 in 12 cases, 1 in 20, and 2 in 10. Table 2 gives the functional condition of these hip joints at present. Two of the patients had operations on both hips; both are much improved and are now walking with canes.



A B

FIGURE 2. *X-Ray Appearance of the Hip in a Fifty-Nine-Year-Old Patient with Osteoarthritis of the Right Hip after a Fall from a Horse Ten Years before* (A) *and after Operation* (B).
The prosthesis with its attached nail (B) *can be seen. The nail projects into the deep cortical bone of the greater trochanter.*

We have been fortunate in having no deaths, severe shock or infection in this group of patients.[25] Table 3 shows the complications observed. There were 5 subluxations of the hip in the early cases until we learned how to prevent them by keeping the hip in internal rotation — all were easily reduced, and no further dislocation occurred. All patients have good functional results. In 2 cases there was slight upward migration of the distal end of the nail. No treatment has been given since so far no symptoms have been caused. Other workers have reported the use of a perforated metal plate attached to the side of the femur for this complication. The nail broke in 1 case six months after operation in the severe fall of an intoxicated patient. The prosthesis was replaced and two years later the patient again had a Grade 1 functional result. One delirious patient got out of bed during the night after operation and separated the sutured gluteal muscles. At reoperation the capsule was already lined with firm fibrous tissue. This patient is steadily improving and is now in Grade 3.

DISCUSSION

Although replacement of the femoral head is a satisfactory procedure for correcting the mechanical faults in many patients with severe osteoarthritis of the hip, no single operation is applicable to all osteoarthritic hips.[26] In every patient rest, support and physiotherapeutic procedures should be tried, but when severe deformity is present only temporary improvement will be observed. If there is severe and increasing deformity and intractable pain, operation should be considered. When the femoral neck is absent another type of prosthesis that replaces the femoral neck may be required, but complete absence of the femoral neck is rare in severe osteoarthritis. All the patients in this series had more than 2.5 cm. of femoral neck remaining,

which permitted the attachment of the prosthesis. All our patients except 4 were in the sixth and seventh decades. Two were in the thirties, and 2 over seventy. Age in itself is no contraindication[27] to surgery of this type if blood loss is replaced and the electrolyte balance is maintained.[28]

Summary

In severe osteoarthritis of the hip joint there are mechanical faults that can be corrected most effectively by replacement of the femoral head with a prosthesis and by correction of the angulation and torsion of the femoral neck. This operation has been performed on 42 severely damaged hip joints with diminution of pain and improvement in function in all cases.

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THE CLINICAL SIGNIFICANCE OF HEMOPTYSIS*

Carlton R. Souders, M.D.,† and Anne T. Smith, M.D.‡

BOSTON

HEMOPTYSIS is an important symptom and often indicates serious disease. Chaves[1] reported that it occurred in 6.8 per cent of all patients seen in an outpatient chest clinic. Abbott[2] found that pulmonary hemorrhage occurred in 38 per cent of 1316 patients with chest disease. Pulmonary tuberculosis is probably the commonest cause for bleeding, and it is estimated that approximately a third of the patients with tuberculosis bleed at some time. About half the patients with carcinoma of the lung have hemoptysis, which, however, is rarely the initial complaint. Over half the patients who have bronchiectasis bleed at some time. However, almost any pulmonary disease may cause bleeding, so that the occurrence of hemoptysis is not, in itself, diagnostic. Occasionally, hemoptysis occurs without a demonstrable cause.

The term hemoptysis is used to designate blood that comes from the respiratory tract at or below the larynx. Bleeding from the oral cavity, nares, pharynx and nasopharynx can usually be identified quite easily. Hematemesis must be excluded by a careful history of the nature of the bleeding episode.

The amount of hemoptysis may vary from a small streak or blood tinge to a massive hemorrhage, but the actual quantity is of little diagnostic importance. However, certain clinical observations may be of some aid in determining the cause of bleeding. Massive hemorrhage is most often caused by tuberculosis, carcinoma or acute pulmonary suppuration. Bleeding of small amounts every day for weeks or months is suggestive of bronchial carcinoma. In a young woman, the history of hemoptysis occurring at intervals for months or years should arouse suspicion of a bronchial adenoma.

The mechanism depends on the type and the location of the disease. If a lesion is endobronchial, the bleeding is from a branch of the bronchial artery or vein. If the lesion is primarily parenchymal, the bleeding is from a branch of the pulmonary artery or vein.

It may be assumed that the frequency of bleeding in patients with chronic bronchial diseases is related to the increased vascularity in the involved areas. This assumption is supported by injection studies[3] demonstrating marked dilatation of the

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bronchial arteries with a rich capillary network surrounding the lesions. Primary malignant growths of the bronchus have this increase in blood supply from the bronchial arteries, but an increased vascularity is not found in metastatic pulmonary neoplasms. Increased vascularity has likewise been demonstrated in chronic tuberculosis, bronchiectasis and cystic disease.

In mitral stenosis the cause of hemoptysis is controversial. It seems to us that the best explanation is that advanced by Ferguson, Kobilak and Deitrick.[4] In the autopsy specimens of patients who had mitral stenosis, injection studies by these authors showed dilated and tortuous varices of the bronchial veins in the submucosa of the larger bronchi. Such varices could well be the source of the profuse hemorrhages that sometimes occur with mitral stenosis.

In congestive heart failure caused by other than rheumatic heart disease the blood spitting may be the result of the high pulmonary venous pressure. This high pressure is also associated with widening of the capillary anastomoses between the bronchial arteries and branches of the pulmonary arteries, but to a lesser degree than in cases of mitral stenosis.[3]

In tuberculosis the mechanism of bleeding varies with the stage, type and location of the disease. First to be considered is hemoptysis that occurs in the acute exudative lesion. As a result of softening of the lung tissue, bleeding comes from necrosis of a small branch of pulmonary artery or vein. The amount of blood is usually small, and although not troublesome in itself, it serves to direct attention to an early lesion that might otherwise go undiscovered.

A second type of bleeding in tuberculosis is pulmonary hemorrhage that occurs in the chronic fibroulcerative type of the disease. It has been demonstrated[5] that this type of hemorrhage often results from the rupture of an aneurysm of an artery traversing the wall of a chronic, thick-walled cavity. Auerbach's[5] studies show that weakness of the vessel wall, caused by tuberculous involvement of the adventitia and media, causes bulging of the vessel into the lumen of the cavity. Under sufficient strain, rupture into the cavity takes place. Hemoptysis due to rupture of an aneurysm into a cavity was first described by Fearn[6] in 1840. The aneurysm is now known as a "Rasmussen's aneurysm," because of the detailed anatomic investigation of patients with hemoptysis made by Rasmussen[7] in 1868.

A third type of bleeding occurs when a healed and calcified tuberculous lymph node impinges on the wall of a bronchus. By the pressure of the hard calcific mass, erosion of the bronchus takes place, with eventual ulceration into the lumen. A broncholith may then be coughed up, usually accompanied or preceded by bleeding. If the node is not completely healed, viable tubercle bacilli are present, and a bronchogenic spread of disease may be produced.

An acute tuberculous ulceration of the bronchial mucosa constitutes still another cause for hemoptysis. Tracheobronchial tuberculosis may be part of a widespread parenchymal involvement or may occur more rarely as a primary bronchial infection. The diagnosis in this case must be made by bronchoscopic examination.

Finally, repeated small hemoptyses occur in patients with tuberculosis whose roentgenograms show small fibrotic or calcific areas, apparently healed. These patients may have no other symptoms and no acid-fast bacilli in the sputum. In such cases it is often possible to demonstrate by bronchography with iodized oil that healing of the tuberculosis has been accompanied by dilatation of bronchi in the involved area. This bronchiectasis frequently occurs in the apical segments and at times persists in spite of an apparently effective thoracoplasty, causing persistent hemoptyses after operation. The bleeding is usually from granulations in the walls of the dilated bronchi that may or may not be tuberculous.

In carcinoma, bleeding results from necrosis of the tumor or invasion of a blood vessel by the growth. Benign adenomas frequently have prominent surface vessels, which can easily be visualized bronchoscopically. Rupture of these friable vessels causes brisk bleeding. Bleeding from pulmonary or bronchial cysts is more difficult to explain but is probably related to the increased vascularity associated with these lesions. In bronchiectasis the destroyed bronchial wall is replaced by granulation tissue, which bleeds easily. If infection is absent and increased vascularity exists, hemoptysis rather than productive cough is the rule. This constitutes the so-called "dry bronchiectasis." In acute bronchitis, the mucosa is unusually vascular and friable, as bronchoscopists frequently observe. Bleeding of considerable amounts may therefore result.

In view of the seriousness of many of the diseases associated with hemoptysis, an attempt should be made in every case to establish the etiology of the bleeding. Yet it is the experience of all who deal frequently with this problem that there are some cases in which a diagnosis cannot be established, regardless of the thoroughness of examination or the length of observation. To study further the clinical significance of pulmonary hemorrhage, we have reviewed the records of the patients who were admitted to the Lahey Clinic over a ten-year period with the *primary complaint* of coughing up blood. Not all patients who bled from the respiratory tract are included, since we have omitted those whose other respiratory symptoms predominated over hemoptysis. Also, we have omitted patients who were referred to the clinic because of abnormal roentgenographic findings. This selection excludes patients with cancer who had chronic cough, pain

or dyspnea as more prominent symptoms or referred because roentgenologic study had demonstrated a suspicious lesion. More than half the patients with bronchiectasis who are seen at the clinic have bleeding, but only a small proportion have hemoptysis as the chief complaint.

The present series includes 105 patients who fulfilled the criterion of blood spitting as the primary complaint. Fifty-seven patients were men, and 48 women. No patient was under twenty years, and over half fell in the group forty to fifty-nine years of age. Sixteen were over sixty years of age.

The amount of the individual hemoptyses varied from a streak to more than half a liter. Most of the patients had expectorated a mouthful or more of blood, but only 6 bled more than 1 cupful. No patient died of pulmonary hemorrhage.

TABLE 1. *Final Diagnoses.*

DIAGNOSIS	NO. OF CASES	PERCENTAGE
Bronchiectasis	30	28.5
Undetermined	19	18.0
Chronic bronchitis	13	12.4
? Bronchiectasis	9	8.5
Rheumatic heart disease	5	4.7
Pulmonary fibrosis	5	4.7
Pulmonary cyst	4	3.8
Hypertension	4	3.8
Carcinoma	3	2.8
Tuberculosis	2	1.9
Acute bronchitis	2	1.9
Polycythemia vera	1	0.9
Anthracosis	1	
Extrabronchial irritation	1	
Acute suppuration (due to *Haemophilus influenzae*)	1	
Chronic pulmonary abscess and bronchiectasis	1	
Granulation tissue	1	
Heart failure	1	
Blood dyscrasia	1	
Atypical epithelial hyperplasia	1	
Total	105	

The number of bleeding episodes before admission varied greatly. We have classified the hemorrhage as a single bout if a definite amount occurred one day, followed by a streaking or a few clots on the next day or two. Nine patients had a single bleeding episode, 47 bled from two to seven times, and 49 had many hemoptyses. About a fourth of the patients had bled at intervals for more than five years before they reported for examination.

The studies in these 105 cases included carefully taken histories, physical and otolaryngologic examination, routine laboratory tests, sputum studies when sputum was obtainable, roentgenograms of the chest, fluoroscopy when indicated, bronchoscopy and bronchograms. In all cases in which the diagnosis could not be made without them, bronchoscopies and bronchograms were advised. In a few cases complete studies were not accepted by the patients. Half the patients had negative physical examinations of the lungs and heart, and yet there were several cases in which the examination, particularly of the heart, was the key to the diagnosis. For example, the discovery of a mitral diastolic murmur led to the diagnosis of rheumatic heart disease, which was confirmed by fluoroscopic study of the heart.

Bronchoscopy demonstrated an abnormality in 54 of the 81 cases in which this study was done. Bronchograms were abnormal in 44 of the 68 cases so studied. The routine plain film or stereoscopic roentgenogram was abnormal in 75 per cent of the cases. This compares with the report by Jackson and Diamond[8] of abnormal roentgenograms in 68 per cent of a series of 436 cases. Although sputum was studied for tubercle bacilli in 40 cases, acid-fast bacilli were not found. In all 3 cases of bronchiogenic carcinoma, tumor cells were demonstrable in expectorated sputum specimens.

Of special interest are the results of the bronchoscopic examinations. In the 54 abnormal bronchoscopic studies, bleeding was seen in 16 cases, abnormal tissue was visualized in 17, and other abnormalities were noted in 21. Ten patients had normal bronchoscopic examinations but abnormal bronchograms, and 7 others had normal bronchograms and yet an abnormality was detected on bronchoscopic examination.

The final diagnoses are shown in Table 1. Bronchiectasis was the most frequent cause of hemoptysis, occurring in 30 cases (28.5 per cent). In a series of patients with hemoptysis studied bronchoscopically, Moersch[9] found bronchiectasis in 26.5 per cent, and in a similar series Jackson and Diamond[8] reported an incidence of 31 per cent. An additional 9 patients in our series were suspected of having bronchiectasis on the basis of clinical and roentgenologic findings, but since bronchograms were not taken, the diagnosis could not be confirmed.

Although tuberculosis is usually considered to be the commonest cause of hemoptysis, this was the final diagnosis in only 2 cases. Many patients with tuberculosis in all stages have been seen during this study, but most of them were referred as special diagnostic or therapeutic problems, or they were asymptomatic and tuberculosis was discovered by routine roentgenograms of the chest.

Bronchiogenic carcinoma was diagnosed in only 3 of the 105 cases. During this period, 351 patients with proved cancer of the lung were seen. Although bleeding occurs at some time in at least half the patients who have cancer of the lung, hemoptysis is rarely the presenting complaint. That 2 of the 3 cases were inoperable serves to emphasize the fact that hemoptysis is a late rather than an early sign of carcinoma.

One can only speculate on the causes of hemoptysis in the patients in whom no definite etiology was found. Some patients may have had an acute infection that subsided; others may have had small bronchial ulcerations beyond the view of the bronchoscopist. Bleeding may come from a small area of bronchiectasis that escapes detection if the

bronchogram lacks technical perfection. Also, a small arteriovenous aneurysm or hemangioma may be missed by all studies, including a bronchoscopy.

No cause of hemoptysis was found in 19 cases (18 per cent) of this series. Of these, 16 patients had bronchoscopic examinations, and 14 had bronchograms. Three of these patients possibly had bronchiectasis, but the studies were incomplete. Two others had hypertension and a third had nasal bleeding, but the relation to the hemoptysis could not be established. One patient had just recovered from an upper respiratory infection, but no disease could be found at the time of examination. In 12 cases in which no possible etiology could be determined 9 patients had bronchoscopic examinations and bronchograms, 1 had bronchoscopic examination alone, and another had only a bronchogram. The twelfth patient had neither bronchoscopic examination nor a bronchogram.

We were particularly interested to determine the fate of these patients in whom all studies failed to reveal a definite diagnosis. No case in which an important lesion was overlooked has been located. After a period of observation ranging from one month to eleven years and averaging twenty-five months, no serious disease has developed. This is in agreement with the recent observation of Moersch[9] in his study of 200 cases of hemoptysis. Furthermore, many of our patients have had little or no additional bleeding.

The treatment in the majority of cases without demonstrable disease consisted of nonspecific medical measures such as the avoidance of tobacco or other irritants, improved general hygiene and the use of expectorants. A few patients were discharged without any treatment. Several patients were given rutin, alone or in combination with vitamin C. Since hemoptysis has usually not recurred during the administration of these drugs, it is our impression (unsupported by controlled observation) that these medications are of use in the symptomatic management of the patient who has frequent small hemoptyses. They have apparently been useful not only in cases in which no etiology could be found but also in bleeding secondary to chronic bronchitis or bronchiectasis.

The treatment of the other cases was determined by the etiology of the bleeding. Pulmonary resection was done in 14 patients with bronchiectasis. Surgical procedures were used in 9 other cases (Table 2). Follow-up studies on the surgically treated patients have shown that hemoptysis has not recurred.

Summary and Conclusions

A definite diagnosis can be made by thorough study and repeated observations in the majority of patients who have pulmonary hemorrhage. In a minority, the exact etiology of hemoptysis cannot be found but, fortunately, serious disease is not likely to develop in these cases.

A series of 105 patients with a presenting complaint of hemoptysis were studied by chest roentgenograms — bronchoscopies in 81 and bronchograms in 68. Bronchiectasis was the commonest cause of bleeding, occurring in 28.5 per cent, and chronic bronchitis was found in 12 per cent. The incidence of tuberculosis (2 cases) and carcinoma (3 cases) was unusually low because hemoptysis was rarely the presenting complaint of patients with these diseases.

In 19 patients (18 per cent) no cause for the bleeding could be determined. Fourteen of these 19 have had a follow-up period of an average of twenty-five months (one month to eleven years). Five cases were lost to follow-up study. In none of those followed has any pulmonary disease developed.

Operation was performed on 23 patients, including 14 cases of bronchiectasis. The results were satisfactory in all. In addition to specific medical measures, rutin and vitamin C were tried, particularly in patients who had repeated minor episodes of hemoptysis, with apparently beneficial results.

Table 2. *Diagnoses in Patients Treated Surgically.*

Diagnosis	No. of Patients
Bronchiectasis	14
Fungous infection	1
Carcinoma:	
Operable	1
Inoperable	2
Tuberculosis	1
Obstructive lesion (atypical epithelial hyperplasia)	1
Pulmonary cyst	2
Pulmonary abscess	1
Total	23

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PASSIVE TRANSFER OF TUBERCULIN SENSITIVITY TO PATIENTS WITH SARCOIDOSIS*

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STUDIES in various countries agree that approximately two thirds of patients with sarcoidosis fail to react to second-strength tuberculin — 0.005 mg. of Purified Protein Derivative (PPD) or 1.0 mg. of Old Tuberculin (OT).[1-3] The failure to react is not merely the result of absence of exposure to tuberculous infection, since patients with sarcoidosis proved unable to develop and maintain tuberculin sensitivity in normal fashion after BCG vaccination.[2, 3] This diminished reactivity to tuberculin has been interpreted as evidence both for[3] and against[1] a tuberculous etiology of sarcoidosis. Two main theories have been proposed to explain this phenomenon:

"Positive anergy" is the term coined by Jadassohn for a specifically acquired immune reaction due to an atypical tuberculous infection manifesting itself as sarcoidosis. It was postulated by Jadassohn[4] and Martenstein[5] that the lack of cutaneous reactivity is due to an equilibrium between antigen and antibody, resulting in rapid removal of the antigen. These authors[6] and others[7] also described specific antibodies ("anticutins") occurring in sarcoidosis that inhibit the skin reaction produced by tuberculin.

The second theory is that the diminished cutaneous reactivity to tuberculin often noted in patients with sarcoidosis is nonspecific and reflects the impaired ability of such patients to form sessile antibodies owing to widespread involvement of the reticuloendothelial system.[1, 2] This theory finds support in other immunologic studies carried out in patients with sarcoidosis. The use of such antigens as pertussis agglutinogen, killed mumps virus and oidiomycin revealed diminished skin reactions in patients with sarcoid as compared to controls.[8, 9] Immunization with pertussis and typhoid vaccines, on the other hand, resulted in normal circulating antibody titers in both groups.[9]

Considerable evidence has accumulated that the antibodies responsible for the delayed, tuberculin type of reaction are produced and carried by cells arising from the reticuloendothelial system.[10-12] It has been possible, with the use of viable leukocytes, to accomplish passive transfer of tuberculin sensitivity to tuberculin-negative recipients, both animal and human.[13, 14] It appeared that the application of this technic to patients with sarcoidosis might clarify the nature of the immunologic defect observed in this disease.

MATERIAL

The study group comprised 6 tuberculin-positive donors, and 5 tuberculin-negative recipients without and 6 tuberculin-negative recipients with sarcoidosis. All subjects had been carefully studied in the outpatient departments of the Henry Phipps Institute and the University Hospital, Philadelphia. The donors and the recipients who did not have sarcoid were free of intercurrent infection, were neither cachectic nor myxedematous and had no clinical, laboratory or roentgenographic evidence of active tuberculosis. The diagnosis of sarcoidosis in the recipients with the disease was made according to the criteria described by Israel et al.[2] The degree of tuberculin sensitivity was established by repeated intradermal testing in all patients and was rechecked two weeks prior to performance of passive-transfer experiments. All tuberculin tests were performed and interpreted according to the standards of the National Tuberculosis Association.[15]

METHOD

Living white blood cells were obtained by a modification of the methods of Minor[16] and Lawrence.[14] The donors were placed in the recumbent position, and a blood-pressure cuff applied to the upper arm and inflated to half-way between systolic and diastolic blood pressure. The skin overlying the median basilic vein was cleansed with alcohol, and a small wheal made over the vein with 4 per cent procaine solution. A No. 16 B-D hypodermic needle, attached to a short piece of rubber tubing, was inserted into the vein, and 50 cc. of blood collected in each of two Lustron centrifuge tubes containing 1 cc. of freshly prepared heparin solution (2 mg. per cubic centimeter). The tubes were immediately closed with rubber stoppers and gently inverted twice. After all donors had been bled, 5 cc. of Seitz-filtered Fraction I (Fibrinogen) solution, containing 45 mg. of Fraction I per cubic centimeter, was added to each tube, and the tubes were again gently inverted twice. Two 50-cc. aliquots of the mixtures so prepared were transferred by pipette to fresh centrifuge tubes, precautions being taken not to wet the wall of the tubes above the meniscus. Immediately after transfer the tubes were sealed with Scotch tape and incubated for an

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hour at 37°C. in a waterbath. At the end of incubation, the supernatant plasma containing the white blood cells was gently pipetted off with a mechanical pipette. Care was taken not to contaminate the plasma with the packed red cells. The white-cell containing plasma was centrifuged in a Servall angle centrifuge at 3000 rpm for an hour. The supernatant was decanted, and the cells washed with 10 cc. of Tyrode's solution (pH of 7.8). The tubes were again centrifuged at 3000 rpm for thirty minutes, and the washing process repeated. The washed cells were resuspended in 1 cc. of Tyrode's solution and injected intracutaneously into the volar skin of the forearm of the recipients. Care was taken throughout to preserve rigidly sterile technic. The time elapsed from bleeding to reinjection did not exceed six hours.

White cells obtained from tuberculin-positive and tuberculin-negative controls were injected into adjacent areas on the forearm of each recipient. Eighteen hours after inoculation, the prepared sites were challenged with 0.005 mg. of freshly mixed PPD.* The reactions were read forty-eight hours after challenge. To determine the duration of the sensitivity produced, the tuberculin test was repeated at a site distant from the cell injection approximately four weeks after the transfer.

Table 1. *Results of Tuberculin Tests after Transfer of Cutaneous Hypersensitivity.*

Donors	Recipients: Tuberculin-negative controls				Patients with sarcoidosis				Tuberculin-positive controls			
	+++	++	+	—	+++	++	+	—	+++	++	+	—
Tuberculin positive	4	2	0	0	5	2	0	0	0	0	0	0
Tuberculin negative	0	2	0	2	0	3	2	2	0	1	0	0
Sarcoidosis	0	0	1	1	0	0	0	0	1	0	0	0

Results

Tuberculin-Negative Recipients without Sarcoidosis

Passive transfer of cutaneous tuberculin sensitivity was unequivocally produced in 6 experiments on 5 tuberculin-negative recipients who did not have sarcoid, confirming the report by Lawrence[14] (Table 1). Of 4 subjects who had sites prepared with cells from tuberculin-negative donors, the challenging tuberculin test was negative in 2 and gave slight ++ reactions† in the other 2. No significant reaction could be demonstrated in two sites prepared with cells obtained from patients with sarcoidosis (Fig. 1).

*Available from Sharp and Dohme, Incorporated, Glenolden, Pennsylvania.

†The slight tuberculin reactions observed in a number of the control sites presumably represented extension of the induced sensitivity away from the initial transfer area (Lawrence[14]). It should also be recognized that to demonstrate passive transfer of cellular sensitivity large quantities of white cells were employed. Transient inflammation occurred after injection of these cells, and in some cases made difficult the interpretation of the reactions after the challenge with tuberculin. Nevertheless, the differences observed between tuberculin-positive and control sites were so marked and consistent (Fig. 1 and 2) that it is clear that actual passive transfer of tuberculin sensitivity was accomplished in every case.

Recipients with Sarcoidosis

Seven areas in 6 recipients with sarcoidosis were prepared with cells obtained from tuberculin-positive donors: all showed strong reactions 48 hours after challenge (Table 1). An equal number of control sites were prepared with cells from tuberculin-negative donors: small ++ tuberculin reactions were noted in 3 subjects, and insignificant reactions in the remainder. In all tests the difference between the tuberculin-positive and the tuberculin-negative cell sites was striking (Fig. 2).

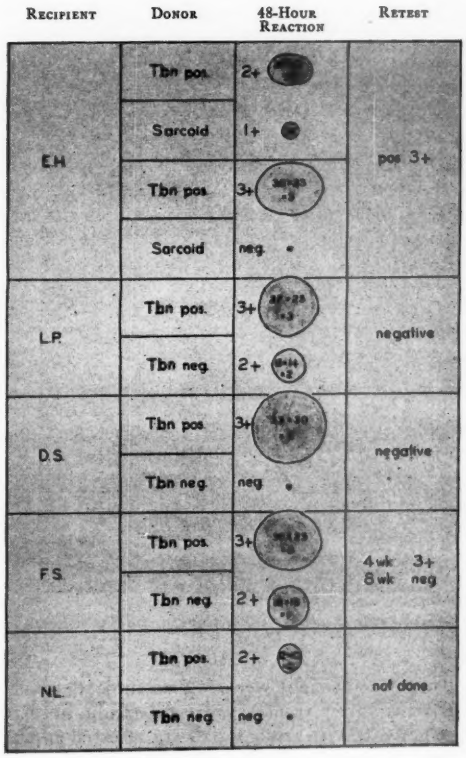

Figure 1. *Passive Transfer of Cutaneous Tuberculin Sensitivity in Tuberculin-Negative Controls.*

Tuberculin-Positive Control Recipient

One tuberculin-positive subject received cells obtained from a tuberculin-negative subject and from one with sarcoidosis. Both areas were strongly positive forty-eight hours after challenge (Table 1 and Fig. 3).

Duration of Induced Sensitivity

Four tuberculin-negative recipients were retested at a site distant from the transfer area. One subject remained positive three weeks after transfer; another was positive when tested at four weeks,

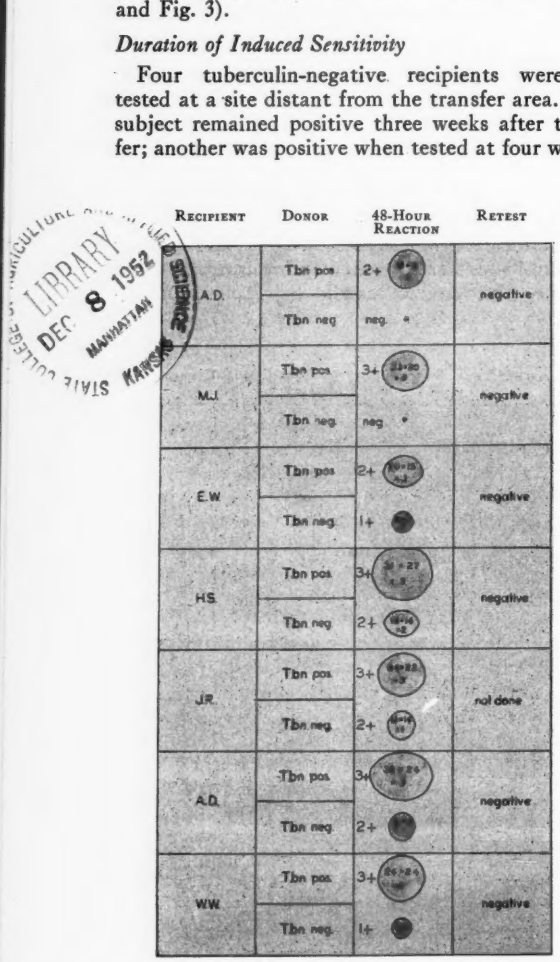

FIGURE 2. *Reactions in Recipients with Sarcoidosis.*

but negative at eight weeks. Two subjects retested four weeks after transfer were tuberculin-negative. Five patients with sarcoidosis were retested approximately four weeks after transfer; all were tuberculin negative.

DISCUSSION

The diminished reactivity of patients with sarcoidosis has been variously explained by the occurrence of anticutins, excessive antibody formation and diminished antibody production. An examination of these theories suggests four possible patterns of response to the passive transfer experiments that we have described:

If "positive anergy" is due to the presence of anticutins in sarcoid skin, no reaction should occur on challenge of transfer sites with tuberculin.

If patients with sarcoidosis are really hypersensitive to tuberculin but their cutaneous reaction is masked by the presence of anticutins, it should be possible to transfer this cellular sensitivity to tuberculin-negative recipients without sarcoidosis.

If anticutins are present in patients with sarcoidosis and are cellular antibodies of the tuberculin type, transfer should be possible to the skin of tuberculin-positive recipients, resulting in a diminished reaction to tuberculin.

If the diminished reactivity is due to the absence of antibodies, the skin of patients with

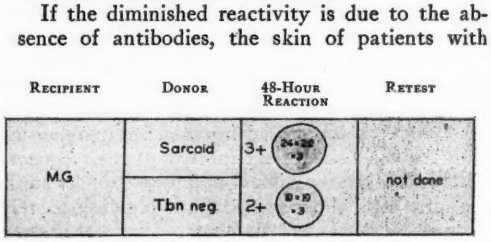

FIGURE 3. *Reactions in Tuberculin-Positive Control Recipient.*

sarcoidosis should behave like that of tuberculin-negative controls, and passive transfer should be successful.

The results of our experiments clearly indicate that it is possible to transfer passively tuberculin sensitivity to the skin of tuberculin-negative patients with sarcoidosis. The strong tuberculin reactions induced by cellular transfer in such patients suggests the absence of anticutins. The failure of sarcoid cells to diminish the tuberculin sensitivity of a tuberculin-positive control is likewise inconsistent with the presence of anticutins. Inability to induce demonstrable tuberculin sensitivity by transfer of sarcoid cells to tuberculin-negative controls provides evidence against Jadassohn's theory that patients with sarcoidosis have a masked hypersensitivity to tuberculin.

It therefore appears that the diminished tuberculin sensitivity of patients with sarcoidosis is best explained on the hypothesis of a deficiency in antibody production or transport.

SUMMARY AND CONCLUSIONS

Passive transfer of tuberculin sensitivity to tuberculin-negative controls was accomplished with the method of Lawrence.

Tuberculin sensitivity was similarly transferred to 6 tuberculin-negative patients with sarcoidosis.

Cells obtained from patients with sarcoidosis did not inhibit the tuberculin reaction in known reactors, nor did they sensitize nonreactors.

The skin of patients with sarcoidosis and that of tuberculin-negative controls responded identically to the cellular transfer of tuberculin sensitivity.

The failure to demonstrate anticutins or other specific inhibiting factors to the tuberculin reaction does not exclude tuberculosis as a cause of sarcoidosis, but does serve to abolish one of the hypotheses on which the belief in a tuberculous etiology has been based. These observations are in better accord with the concept that tuberculin anergy in sarcoidosis is nonspecific and due to involvement of the reticuloendothelial system by the disease.

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THE HEPATOTOXICITY OF INTRAVENOUS AUREOMYCIN*

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BOSTON

THIS report deals with hyperbilirubinemia developing during the intravenous administration of aureomycin in a series of 39 patients. To determine the relation of intravenously administered therapeutic doses of aureomycin to this disorder the effect of the drug on normal liver function was studied in 20 selected patients with no evidence of cardiovascular, renal, hepatic or biliary-tract disease. Each patient received aureomycin (500 mg. of the hydrochloride buffered with sodium glycinate, dissolved in 500 cc. of isotonic sodium chloride) intravenously twice a day for three consecutive days. Serum bilirubin§ and urinary uro-

Table 1. *Data in 20 Patients with Normal Hepatorenal Function Who Received Aureomycin.*

Case No.	Serum Bilirubin*			Urinary Urobilinogen	Bromsulfalein Retention		Cephalin Flocculation	
	Before Therapy	During Therapy	After Therapy		Before Therapy	After Therapy	Before Therapy	After Therapy
	mg. per 100 cc.	mg. per 100 cc.	mg. per 100 cc.		%	%		
1	0.6	1.8	—	Normal†	—	—	—	—
2	0.2	1.6	0.6	Negative	2.0	9.0	+	+
3	0.8	1.4	0.7	Negative	—	—	—	—
4	0.6	1.4	0.9	Negative	—	—	—	—
5	0.9	1.3	1.2	Normal	9.0	23.0	+	++
6	—	1.2	0.2	Negative	2.0	5.0	+	+
7	0.7	1.2	0.4	Normal	—	—	—	—
8	0.6	1.2	0.4	Normal	—	—	—	—
9	0.6	1.0	—	Normal	3.5	16.0	++	++
10	0.4	0.9	0.6	Elevated‡	—	—	—	—
11	0.2	0.9	—	Normal	—	—	—	—
12	0.8	0.9	—	Normal	—	—	—	—
13	0.7	0.8	0.5	Normal	—	—	—	—
14	0.6	0.8	0.4	Normal	—	—	—	—
15	0.5	0.8	0.9	Normal	6.0	33.0	+	++
16	0.5	0.8	0.6	Normal	8.0	13.0	+	++
17	0.4	0.7	0.6	Negative	2.0	3.0	+++	++
18	0.4	0.3	—	Normal	—	—	—	—
19	0.6	0.3	0.3	Normal	—	—	—	—
20	0.8	—	0.5	Normal	—	—	—	—

*Average of 1 to 3 determinations.
†Positive in dilution of 1:10.
‡Positive in dilution of 1:80.

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§Serum bilirubin concentrations were determined by the Mallory and Evelyn[1] colorimetric technic. Normal values by this method vary from 0.2 to 0.8 mg. per 100 cc., with a mean of 0.6 mg. as determined by a series of 150 consecutive serum bilirubin determinations in this hospital in 1950-51.

bilinogen[2] excretion were determined in all 20 patients. Serum bilirubin concentrations were determined daily and in several cases twice daily. In most cases two or three values ranging from 0.2 to 0.8 mg. per 100 cc. were obtained prior to administration of aureomycin. In 7 patients bromsulfalein retention and cephalin flocculation were determined, before, during and after aureomycin therapy.

TABLE 2. *Hyperbilirubinemia Developing after Operation and Intravenous Administration of Aureomycin.*

OPERATION	TOTAL NO. OF PATIENTS	PATIENTS SHOWING HYPERBILIRUBINEMIA
Gastrectomy	22	7
Resection of colon	20	8
Resection of small bowel	3	3
Miles resection	13	2
Closure of colostomy	3	2
Appendiceal peritonitis	11	2
Closure of perforated peptic ulcer	4	2
Esophagectomy	2	1
Colotomy	3	1
Ventral herniorrhaphy	8	2
Totals	89	30

In 9 patients (Table 1) transient hyperbilirubinemia developed after 2 or 3 gm. of aureomycin had been given, but disappeared within forty-eight hours of discontinuance of the drug. In all cases in which hyperbilirubinemia was recorded there was a clear-cut elevation of serum bilirubin concentration eighteen to forty-eight hours after onset of aureomycin therapy, and a rapid and progressive decline subsequent to termination of therapy. In several of these patients serum bilirubin was again measured ten to thirty days later and failed to reveal any values above 0.8 mg. per 100 cc.

Urobilinogen disappeared from the urine in 5 of the 20 patients after three days of aureomycin administration. This has been related to the suppression of the intestinal bacteria responsible for the conversion of urobilin to urobilinogen.[3, 4]

Abnormal bromsulfalein retention developed in 4 of the 7 patients in whom this test was performed. The cephalin flocculation remained normal in all cases.

Eighty-nine patients received the same dose of aureomycin intravenously after operation (Table 2). Seven of them also received 1.5 to 2.0 gm. a day orally for two to seven days before operation. In none was there any evidence of disease that might have caused impaired liver function, although 61 patients had had blood transfusions, usually on the day of operation, without noticeable reaction.

TABLE 3. *Data in 30 Patients with Hyperbilirubinemia after Operation and Intravenous Administration of Aureomycin.*

CASE NO.	OPERATION	AUREOMYCIN THERAPY			INTERVAL BETWEEN OPERATION AND OCCURRENCE OF HYPERBILIRUBINEMIA	SERUM BILIRUBIN	JAUNDICE		LIVER-FUNCTION TESTS DURING HYPERBILIRUBINEMIA
		ROUTE	DURATION	TOTAL DOSE			OCCURRENCE	DURATION	
			days	*gm.*	*days*	*mg. per 100 cc.*		*days*	
1	Resection of ileum	Intravenous	2	2	2	3.6	Present	5	—
2	Resection of ileum	Intravenous	2	2	2	1.0	Present*	2	—
3	Herniorrhaphy	Intravenous	2	3	2	1.1	Absent	—	—
4	Revision of colostomy	Oral	7	14	3	1.2	Absent	—	—
		Intravenous	2	2					
5	Miles resection	Intravenous	3	3	3	1.4	Absent	—	—
6	Resection of colon	Intravenous	3	3	3	1.2	Absent	—	—
7	Gastrectomy	Intravenous	3	3	3	1.1	Absent	—	—
8	Appendectomy and sigmoidotomy	Intravenous	3	3	3	2.5	Absent	—	Normal
9	Gastrectomy	Intravenous	3	3	3	1.2	Absent	—	—
10	Gastrectomy	Intravenous	3	3	6	1.5	—	—	—
11	Appendectomy	Oral	2	3	5	7.6	Present	5	Abnormal
		Intravenous	3	3					
12	Resection of colon	Oral	7	14	4	4.3	Present	5	—
		Intravenous	3	3					
13	Appendectomy	Intravenous	4	6	5	1.4	Absent	—	—
14	Right colectomy	Oral	6	12	6	3.9	Present	4	—
		Intravenous	4	4					
15	Right colectomy	Oral	5	10	4	2.0	Present	3	—
		Intravenous	4	4					
16	Herniorrhaphy	Intravenous	5	5	4	1.2	Absent	—	Normal
17	Gastrectomy	Intravenous	5	5	5	1.4	Absent	—	—
18	Right colectomy	Intravenous	5	5	5	1.2	Absent	—	—
19	Closure of perforated ulcer	Intravenous	5	5	5	3.1	Present	6	Normal
20	Gastrectomy	Intravenous	5	5	6	1.4	Absent	—	—
21	Esophagectomy	Intravenous	5	5	6	3.5	Present	7	Abnormal
22	Resection of colon	Oral	5	5	5	2.6	Present	5	Abnormal
		Intravenous	5	5					
23	Resection of colon	Intravenous	6	6	6	1.2	Absent	—	—
24	Gastrectomy	Intravenous	6	6	6	1.9	Absent	—	Normal
25	Resection of ileum	Intravenous	6	6	6	2.9	Present	3	—
26	Gastrectomy	Intravenous	7	7	7	5.2	Present	5	—
27	Closure of colostomy	Intravenous	7	7	7	3.0	Present	5	Abnormal
28	Resection of colon	Intravenous	7	7	7	2.1	Present	3	—
29	Miles resection	Oral	3	6	7	4.7	Present	5	—
		Intravenous	7	7					
30	Closure of perforated ulcer	Intravenous	9	9	9	1.9	Present	10	—

*Serum bilirubin determined 2 days after jaundice had been observed.

Thirty of these 89 patients manifested hyperbilirubinemia* usually three to seven days after operation (Tables 2 and 3). Sixteen received a transfusion, usually on the day of operation. Fourteen received no blood at any time.

In 16 patients the hyperbilirubinemia was of a low order (bilirubin level of less than 2.1 mg. per 100 cc.). Three of these patients were icteric.† The remaining 14 patients showed bilirubin levels greater than 2.0 mg. per 100 cc. Of these, 12 were icteric. Jaundice occurred in 6 of the 7 patients who received aureomycin before operation. The hyperbilirubinemia was transient in all 30 patients, and serum bilirubin levels, measured daily, progressively returned to normal about three to five days after the drug had been discontinued.

Thymol-turbidity‡ and cephalin-flocculation tests were performed in 8 cases after onset of hyperbilirubinemia. Four showed abnormalities (cephalin flocculation, +++; thymol turbidity, 9.5–19.5 units), which were as transient as the hyperbilirubinemia. All tests yielded normal values 3 to 10 days after stopping the drug.

Normal serum with aureomycin concentrations varying from 1 to 200 microgm. per cubic centimeter was tested for bilirubin in order to determine whether the drug can produce a false-positive test. Concentrations of aureomycin achieved in the blood with therapeutic dosages given intravenously are about 5 to 10 microgm. per cubic centimeter.[7-9] At high serum concentrations of aureomycin (50 to 100 microgm. per cubic centimeter) bilirubin levels were raised by 0.2 to 0.3 microgm. per cubic centimeter because of the yellow color of the drug. There were no false-positive reactions. These experiments, however, do not rule out the possible presence of degradation products in vivo and their role in the test for bilirubin. In other experiments it was shown that aureomycin, in vitro, does not interfere with the colorimetric determination of serum bromsulfalein retention.

Discussion

Abnormalities in liver-function tests, including hyperbilirubinemia, are frequently detectable during the first twenty-four hours after operation in patients with normal liver function who have not received aureomycin.[10-16] These usually disappear by the fifth postoperative day. The variations observed are largely independent of the type of operation or the anesthetic agent used. Clinical icterus is never observed.

The abnormalities in liver-function tests observed postoperatively in the 30 patients were not entirely of this pattern because hyperbilirubinemia developed more than two days after operation in all but 3 cases and four to seven days after operation in 21 of the 30 patients, 15 patients showed clinical icterus and hyperbilirubinemia persisted in all cases until aureomycin was discontinued, disappearing shortly thereafter.

Furthermore, the development of hyperbilirubinemia and other abnormalities in liver-function tests in the nonoperative group of 20 patients indicates that aureomycin alone is responsible for these changes. Indeed, liver injury has been observed in man and animals after oral as well as intravenous administration of aureomycin.[17-19]

The foregoing data suggest that operative stress potentiates the effect of aureomycin on the abnormalities in liver-function tests. This has been observed with other hepatotoxic agents.[20]

The toxic effect of intravenously administered aureomycin, however, was always mild and transitory. Administration of the drug to patients with jaundice and severe liver damage due to cholangitis or suppurative hepatitis resulted in improvement in liver function after prompt control of the infection.[21, 22] Aureomycin is also said to be useful in the treatment of hepatic coma.[23]

Hyperbilirubinemia has not been noted in patients receiving aureomycin orally in the usual dosage. This may be due in part to the lower concentration of the drug in the blood and tissues after oral therapy than is achieved with intravenous administration.

Addendum

Since liver injury has been observed after terramycin,[18, 19] similar changes in liver-function tests after terramycin therapy might be expected. We can present no pertinent data on terramycin, because the prohibitive incidence (30 per cent) of serious gastrointestinal reactions that followed intravenous as well as oral therapy precluded the administration of the drug to normal or postoperative patients for the purpose of evaluating its effects on liver function.

Conclusion

The data presented demonstrate that aureomycin administered intravenously to postoperative patients can produce transient clinical icterus, which can be differentiated from icterus from other causes by the observation of its prompt disappearance after the drug has been discontinued.

*Serum bilirubin was determined at intervals of one to three days before the administration of the morning dose of aureomycin.

†Serum bilirubin concentrations of 1.2 mg. per 100 cc. or higher are said to result in icterus of the skin and scleras.[5]

‡Determined spectrophotometrically by a modification of MacLagen's method.[6] Normal values range from 4 to 8 units.

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MEDICAL PROGRESS

THORACIC SURGERY

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THIS report considers the following aspects of thoracic surgery; anatomy; physiology; cancer of the lung; tuberculosis; empyema; bronchiectasis; lung abscess; spontaneous pneumothorax; pectus excavatum; and the esophagus.

ANATOMY

When the last Progress Report on thoracic surgery appeared in this journal, virtual agreement had been reached in the matter of disposition and nomenclature of the bronchopulmonary segments. This agreement became apparent in 1949, when the American Association for Thoracic Surgery officially adopted the Jackson-Huber terminology.[1] In the following year an International Committee nominated by the Thoracic Society of Great Britain formally accepted and published a similar although not identical nomenclature.[2] There the matter rests. The terminology adopted by the latter group is here recorded as follows:

	Upper Lobe	
	1. Apical	
	2. Posterior	
	3. Anterior	
Middle Lobe		*Lingula*
4. Lateral		4. Superior
5. Medial		5. Inferior
	Lower Lobe	
	(R)	(L)
6. Apical		6. Same
7. Medial basal		
8. Anterior basal		8. Same
9. Lateral basal		9. Same
10. Posterior basal		10. Same

The validity of the terminologies adopted has been further established in the studies of Boyden and his associates.[3-8] By careful analysis of the anatomic variations of the segmental bronchi and their related blood vessels, they have determined prevailing patterns and major variations.[9] These studies are now complete for all five lobes and are readily accessible.

Interest in the gross anatomy and embryology of the lung has been greatly enhanced by a clinical entity that Pryce et al.[10] have called "intralobar sequestration of lung associated with an abnormal pulmonary artery." The term requires some clarification. It refers to a cystic mass that lies within the substance of either lung in relation to the pulmonary ligament. The mass is supplied by a large primary branch of the aorta, a matter of obvious surgical significance when resection is undertaken. Infection in such cysts is of great clinical importance although gross communication with the bronchial tree may be difficult to demonstrate. Pryce has attempted to explain the anomaly according to the following hypothesis. A persistent artery from the dorsal instead of the ventral aorta to the pulmonary anlage attaches itself to one of the bulbous growing tips of the budding bronchi and there enters into competition with the developing pulmonary artery. As the embryo grows and straightens, and as the lung shifts into a more cephalad position, the captive bulb is gradually torn away and isolated (sequestered), producing rests from which cysts may develop. The anomalous artery usually has many of the physical characteristics of a pulmonary artery, and these render it a relatively fragile vessel to carry blood at systemic pressure.

Pryce, Sellors and Blair[10] described 8 cases of sequestrated lung in 1947, and many series have subsequently been reported.[11-15] A case discussed in this journal in 1950[16] provides an excellent description of the clinical picture and the gross pathology. In this case it was possible to demonstrate clearly that anastomoses were present between the systemic

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artery and the pulmonary artery to the affected segments.

So far as is known, cystic changes in the lung are not associated with anomalies of the pulmonary veins, although Drake and Lynch[17] have reported a case in which bronchiectasis of the right lower lobe was associated, probably fortuitously, with a lower-lobe vein that drained directly into the inferior vena cava. Brantigan[18] has discussed the subject of anomalous venous drainage of the lung at some length. He estimates that a normal heart can tolerate up to 50 per cent of an abnormal venous return from the lung into the right atrium or the venae cavae. The diagnosis can be made by angiography and by cardiac catheterization, as Cooke et al.[19] have shown. It is of interest that creation of this abnormality is one step in the operation that Blalock and Hanlon[20] have proposed for transposition of the great vessels.

It is certain that a greater number of vascular anomalies of the lung will be recognized as angiocardiography is more widely used in the study of difficult chest problems. Steinberg and his associates[21] have demonstrated the utility of the method and also its safety in over 1000 cases. Contrast visualization of the pulmonary and mediastinal blood vessels by Diodrast or a similar compound not only is useful in the differentiation of vascular abnormalities from mediastinal tumors but also may, on occasion, be of value in the early diagnosis of pulmonary neoplasms,[22] of which Nabatoff[23] has described an excellent example. Worthy of further study is the claim of Keil and Schissel[24] that pulmonary angiography may be most helpful in distinguishing between primary bronchogenic carcinoma and "resolving or unresolved" pneumonia. In a series of 26 patients with bronchogenic carcinoma, they found decreased vascularity of the lesion in question in 24, whereas in 35 patients with "resolving or unresolved" pneumonia, vascularity was increased in all. On the other hand, decreased vascularity in tuberculosis foci is well known, and this too has been demonstrated by angiocardiography.[25, 26]

Physiology

The role and importance of collateral circulation in the lung has been the subject of extensive study in the past few years. This has been admirably reviewed by Liebow and his associates,[27, 28] who have clearly demonstrated that in chronic pulmonary disease, notably bronchiectasis, gross precapillary anastomoses are formed between the bronchial arteries and the pulmonary arteries. In congenital heart disease these anastomoses are found relatively close to the hilus; in bronchiectasis they are at the level of third-order and fourth-order branching of the lobar arteries. The physiologic implications of these anastomoses are enormous. In the first place, this collateral may present a physiologic block to the perfusion of an unaerated or poorly ventilated segment by unsaturated blood. In the second place, it represents a shunt between the aorta and left atrium and thus imposes a greater burden upon the left ventricle. This may help explain the degree of hypertrophy of the left ventricle that is often found in association with cor pulmonale. To support the validity of these concepts, Liebow and his associates present cardiac-catheterization data of a patient who had extensive bronchiectasis involving the entire left lung. Blood taken from the left pulmonary artery under conditions that precluded sampling of capillary blood had an oxygen content approximately that of systemic arterial blood. Blood from the right pulmonary artery had an oxygen content considerably lower than that in the left, a difference well outside the limits of experimental error. A less striking pressure differential was observed between the two sides. Subsequent plastic injection studies of this left lung after its removal showed it to have many large anastomotic channels.

Gilroy, Wilson and Marchand[29] present supporting evidence obtained during operation on 3 patients with bronchiectasis. Although their findings are subject to the limitations imposed by an open chest and sampling by suction into a syringe, it is interesting that in all 3 patients blood in the branch of the pulmonary artery to the affected lobe showed a 95 to 100 per cent oxygen saturation. This they interpreted as showing reverse flow and a physiologic blockade.

The observation of great increase in the size of the bronchial arteries to chronically or acutely infected lobes is not a new one, but elucidation of the changes in hemodynamics of such lobes is highly important. Churchill[30] has called attention to the fact that these alterations may exist in the absence of clinically significant infection — for example, in the scarred lobe or segment of obliterative bronchitis. He points out that "unless this increased volume flow of arterial blood meets some functional demand, it would appear as an exception to John Hunter's principle of minimal work, according to which arterial supply is carefully rationed 'to keep a circulation sufficient for the part, and no more.'"

Cockett and Vass[31, 32] have studied, as Liebow et al. did, the enormous collateral circulation that develops by way of the bronchial arteries after ligation of the main pulmonary artery on one side. Such a collateral soon becomes sufficient to sustain life under conditions of high oxygen in the inspired air when the contralateral bronchus is occluded.

Perhaps one of the greatest advances in studies of pulmonary function in the past few years has been a standardization of definitions and symbols.[33] Total lung capacity is now subdivided as follows:

(1) tidal volume, (2) inspiratory capacity (formerly, complemental air, which is measured

from pulmonary mid-capacity or the point at the end of normal expiration), (3) expiratory reserve (formerly, supplemental air), (4) residual volume (measured from the point of maximum expiration), and (5) functional residual capacity (measured from pulmonary mid-capacity). Vital capacity equals the sum of (2) plus (3).

Gaensler[34, 35] has added two useful clinical indexes of ventilatory function: timed vital capacity and air-velocity index. The former, by introducing a time factor into the measurement of vital capacity, achieves the same characterization of function that can be obtained by measurement of maximum breathing capacity, which is the maximum ventilation that can be accomplished voluntarily in a given unit of time, usually stated as liters per minute. In a timed vital capacity, the fatigue factor is eliminated, however, and co-operation on the part of the subject is perhaps easier to obtain. Air-velocity index represents "a numerical expression of the functionally effective portion of ventilation." It is simply a statement of the ratio:

$$\frac{\text{per cent of predicted maximum breathing capacity.}}{\text{per cent of predicted vital capacity}}$$

Normally, this ratio should be 1.0. When it is less than 1.0 the ventilatory deficit is usually the result of bronchial obstruction or loss of elasticity of the lung, or both. When the ratio is greater than unity, the defect is usually the result of loss of pulmonary tissue or collapse. This evidence may be useful to confirm a clinical impression. In such measurements, however, it is extremely important to distinguish between ventilatory and pulmonary function, which includes respiratory function, and to recognize the many variables that are being measured.

The subject of pulmonary-function tests has been critically reviewed in the second volume of *Methods in Medical Research*, edited by Comroe.[36] It is immediately obvious that all measurements of pulmonary function demand exacting attention to details of technic. As an investigative tool the methods presently available may have fundamental significance, as the work of Cournand and his associates[37] testifies. For example, measurement of the diffusion characteristics of the alveolar membrane is of immense importance to the study of pulmonary disease and hence to thoracic surgery. Equally significant are the perfusion relations between pulmonary circulation and alveolar ventilation.

The immediate need for accurate measurement of pulmonary function is seen in the present status of autonomic surgery for the relief of asthma. As Blades et al.[38] have succinctly phrased it, one is faced with "the bewildering consequences of an empirical surgical approach." Thus, they found that, of 32 patients in whom a complete denervation of the left lung was carried out, 11 were asthma free, and 6 were dead, and in 15 the results were equivocal. Klassen, Morton and Curtis[39] reported that, of 3 patients subjected to bilateral vagus resection for intractable bronchial asthma, 1 was "cured," 1 was unchanged, and 1 was dead. Abbott and his associates[40] have described 72 patients in whom sympathectomy or some type of "pulmonary plexectomy," with or without the resection of "trigger areas," was carried out after conservative measures, including psychotherapy, had been exhausted. The results were far from conclusive.

One cannot leave the subject of pulmonary physiology without calling attention to the interesting studies of bronchial pain and its abolition by section of the vagus nerve that Morton, Klassen and Curtis[41-43] have reported. They observed that electric stimulation of a major bronchus by an endoscopic electrode produced pain of an aching character referred to the corresponding anterior chest wall. This pain was abolished by section of the homolateral vagus nerve distal to the origin of the recurrent nerve. At the same time, cough in response to this stimulus was abolished, although clearing of Lipiodol, and hence presumably of secretions, was not impaired. The implications of these observations in the treatment of distressing pain and cough in cases of inoperable carcinoma should be further explored.

The physiologic background for the intelligent management of severe chest injuries was so completely worked out and tested in World War II that little has been added to the subject. One addition, however, has been the more widespread use of tracheotomy in crushing injuries to the thorax and after extensive intrathoracic operations in which the integrity of the chest wall is badly compromised. Carter and Giuseffi[44] have skillfully presented the argument for tracheotomy under these circumstances. They suggest that the benefits arise from easier access to bronchial secretions, reduction of the anatomic dead space and decreased resistance to inspiration and expiration, with consequently less paradoxical motion of the chest wall. Reynolds and his associates[45] recommend tracheotomy in patients undergoing resection for high esophageal lesions — not in every patient, but promptly in those in whom excessive rhonchi are heard immediately or soon after operation. With these opinions I strongly concur.

Serious injury to major bronchi is uncommonly recognized as a complication of serious chest injury. Kinsella and Johnsrud[46] have reviewed the subject thoroughly and have collected more than 20 reported cases of patients who survived the immediate effects of bronchial rupture but in whom atelectasis or destructive infection distal to a bronchial stricture later developed. Griffith[47] and Paulson[48] have each described plastic repair of such strictures, with salvage of the distal lung. In 1 case at the Massachusetts General Hospital

immediate thoracotomy for uncontrollable tension pneumothorax after an automobile accident disclosed rupture of the right main bronchus.[49] This was easily repaired, with an excellent functional result.

Cancer of the Lung

Cancer of the lung continues to dominate thoracic surgery, in terms of both its cause and its control. For many years the relation between smoking and cancer of the lung has been widely investigated. The question was recently the subject of an address by Evarts Graham[50] before the Boston Surgical Society on the occasion of his receiving the Bigelow Medal. Graham states the argument thus. The actual increase in primary carcinoma of the lung has been so startling as to require explanation. In current civilization, cancer of the lung has come to rival and, in many hospital populations, to exceed cancer of the stomach in frequency. One can reasonably postulate that the people of the western world have exposed their lungs during the last thirty-five or forty years to some exogenous carcinogenic factor to a greater extent than previously. Furthermore, in view of the pronounced incidence of the disease among men, one can postulate that men have been exposed to this factor more than women. Among the many exogenous factors that can be suggested, cigarette smoking, in which there has been a more or less parallel increase, appears the most likely. Statistical support, however, is needed. This Graham and his associates[51] find in a study of 684 proved cases of carcinoma of the lung. Representative figures are as follows. Of 605 male patients with lung cancer, 51 per cent were excessive or chain smokers. Of 780 male controls (that is, patients of corresponding ages admitted to Barnes Hospital) only 19 per cent were excessive or chain smokers. Only 2 per cent of the 605 were nonsmokers. Of all patients with carcinoma of the lung, 96 per cent had smoked for more than twenty years.

Support for Graham's thesis can be found in the careful statistical study by Doll and Hill,[52] which subsequently became the subject of an editorial in the *Lancet* entitled "Smokers Beware!"[53] Doll and Hill were impressed by the fifteen-fold increase in the annual number of deaths from cancer of the lung in Great Britain from 1922 to 1947. Presumably this was a real increase, although it was impossible to determine how much was the result of improved methods of diagnosis and reporting. To study the problem, they enlisted the co-operation of 20 major London hospitals. All patients admitted to these hospitals with a diagnosis of cancer of the lung were interviewed by a social worker, who at the same time interviewed a "control." As the authors point out, it is not always easy to elicit an accurate smoking history or, for that matter, to define a "smoker." This they characterized as a person who had smoked as much as 1 cigarette a day for as long as a year. Approximately 709 patients with carcinoma of the lung were involved in the study. Only 0.3 per cent of male patients with cancer of the lung were nonsmokers, whereas 4.2 per cent of the male "controls" did not smoke. Thirty-one per cent of female patients with primary cancer of the lung and 53 per cent of the female "controls" were nonsmokers. Among the patients with pulmonary cancer there was a significantly greater proportion of heavy smokers. Doll and Hill found that by whatever measure of smoking they used, there was a significant and clear relation between smoking and cancer of the lung, with one rather surprising exception: there was no significant correlation between whether the cigarette smoker inhaled or not.

So far as control of cancer of the lung is concerned, the thoracic surgeon is perhaps more interested in early diagnosis and evaluation of the results of his surgical treatment than in changing the social habits of his patient. Toward earlier diagnosis he has been greatly aided by the increased awareness on the part of the medical profession and the public of the early symptoms of cancer. The evidence that mass x-ray surveys have contributed to this improvement is not so clear. In this regard, the report of the recent Chest X-Ray Survey in the City of Boston[54] is of great interest. In this study, 536,012 patients were surveyed by small films. Of these small films, 9372 were sufficiently suggestive to warrant a conventional large chest film. Of the 9372, 398 were classified as suggestive of cancer, but in only 76 of these "cancer suspects" was a diagnosis of cancer eventually established. Of the 76, 43 were proved to have primary cancer of the lung. The surgical fate of these 43 is interesting. Thirteen lesions were deemed inoperable. In 8 surgery was limited to exploratory thoracotomy. Two patients refused operation. Resection was possible in only 20 patients. The long-term survival of this group is not known. Also unknown is the number of patients in whom, by reason of a survey film, exploratory thoracotomy was considered necessary and in whom something besides malignant neoplasm was found. If the report by Abeles and Ehrlich,[55] based on New York City surveys, is a guide, it is probable that this number is considerable. Without stating the total number of patients involved, these authors report 44 cases of single, circumscribed intrathoracic densities picked up in a mass survey. Exploratory thoracotomy was advised in 31 and was carried out in 21 patients, of whom only 5 had primary carcinoma of the lung; there were 5 "tuberculomas," 2 chronic lung abscesses, 1 "lipoid pneumonia," 1 pericardial cyst and other benign lesions.

At the present time, when any suspicious shadow in a chest film leads to surgical consultation to exclude cancer that "cannot be ruled out," it is worth while to consider some of the other diagnostic possibilities. Waddell, Sniffen and Sweet[56] have dis-

cussed the clinical and pathological importance of chronic pneumonitis and have reported 10 cases of interstitial pneumonitis with unusual cholesterol deposits. Although it would be of obvious importance in the differential diagnosis of cancer, they could find no clear distinguishing characteristic before operation. Shaw[57] has described 10 patients in whom mucoid impaction of the bronchus produced a radiologic picture easily confused with neoplasm, often to the extent of making exploration mandatory. The disease, however, was in fact a complication of asthma or chronic obstructive bronchitis. Berg and Burford[58] have pointed out that pulmonary paraffinoma, so-called "lipoid pneumonia," which is generally associated with the prolonged and excessive use of oily nose drops or mineral oil by mouth, may produce a pulmonary lesion that not only is indistinguishable from cancer radiologically but also may be confusing at the time of exploratory thoracotomy. Graham, Burford and Mayer,[59] Paulson and Shaw,[60] and Brock[61] have called attention to the so-called "middle-lobe syndrome" — namely, chronic atelectasis and pneumonitis of the middle lobe associated with chronic lymphadenitis that is usually of tuberculous origin; the involved lymph nodes encroach upon the middle-lobe bronchus, which is vulnerable by reason of its great length and position. The difficulty in distinguishing carcinoma from focal areas of tuberculosis is well known and is considered at greater length below.

Resection remains the optimal treatment for cancer of the lung, and it is surprising how closely the results of treatment agree in the published reports of different surgeons and clinics. If resection is possible, a five-year survival rate of 25 to 30 per cent can reasonably be expected. In closing what had been a lively debate upon the relative merits of lobectomy and pneumonectomy for cancer, Churchill[62] pointed out that "the prowess of the surgeon, assuming a reasonable degree of competence, is probably the least significant of all the variables. We are all doing about the same job with about the same results." There is reason for great optimism in the early case, or what Overholt[63] has termed the "silent phase" of cancer of the lung.

It is possible that more extensive dissections of hilar lymph nodes as a part of pulmonary resection will significantly improve the survival rate for carcinoma. Weinberg[64] has applied to the lung his method of demonstrating regional lymph nodes by vital staining with pontamine sky blue. He has confirmed the lymphatic drainage of the lung that Rouviere[65] described in 1938. Weinberg advocates a method of "radical" pneumonectomy designed to remove maximal amounts of satellite lymphatic tissue *en bloc* with the lung. Cahan, Watson and Pool[66] likewise provide an excellent discussion of the technic of mediastinal-lymph-node dissection and describe its use in 39 cases of cancer of the lung. In 18 of these patients, metastatic tumor was discovered in lymph nodes beyond the limits of the average "simple" pneumonectomy. The authors do not advocate routine intrapericardial ligation of the pulmonary vessels, a measure that Allison[67] has recommended and described. Healey and Gibbon[68] have also discussed and illustrated intrapericardial anatomy in relation to pneumonectomy.

McCort and Robbins[69] have described the radiologic pattern of lymph-node metastasis in cancer of the lung. Their report is based upon 103 proved cases in which radiologic observation could be correlated with operative findings. They could identify the following groups of lymph nodes: lobar, interlobar bronchial and arterial, hilar, right paratracheal, left paratracheal (difficult to visualize), bifurcation, posterior mediastinal, left prevascular and right prevascular. This grouping of nodes is comparable to that of Rouviere, whose work was cited above.

A group at the Mayo Clinic[70-73] has reported the results of surgical treatment of carcinoma of the lung according to pathological cell type. In the squamous-cell and the large-cell carcinoma group, they found the highest resectability rates. Adenocarcinoma was less often amenable to resection but, if resected, bore a reasonably optimistic prognosis — in their experience, about 30 per cent survival for more than two years. Bronchogenic small-cell carcinoma, they found, was infrequently resectable and rarely curable. These results conform to the general experience with the disease, particularly so far as small-cell or oat-cell carcinoma is concerned. It is fortunate that for the latter group radiation therapy is reasonably effective.

The difficulty of arriving at diagnosis of a single cell type has been clearly demonstrated by Phillips, Basinger and Adams.[74] Using large, "total-tumor" mounts in the study of 40 cases, they found that any combination of cell types might exist within a given tumor, except that they did not find squamous cells with pearl formation associated with adenocarcinoma. No particular cell type predominated in peripheral lesions. McGrath, Gall and Kessler[75] have confirmed this work and also demonstrated multiple foci of preinvasive carcinoma in a significant proportion of lung tumors studied by large tissue sections.

Of great interest among the histologic types of cancer of the lung is alveolar-cell carcinoma or pulmonary adenomatosis. Morphologically, this is almost identical with jagziekte, an infectious disease in sheep. Delarue and Graham[76] accept the concept that it is a multicentric tumor of epithelial origin, presumably arising from the epithelial cells that line the alveoli. Potts and Davidson[77] disagree and report a carefully studied case in which they conclude that, in this patient at least, they were dealing with a bronchogenic adenocarcinoma masquerading as an alveolar-cell tumor. Stephens and Shipman[78] report a case in which the diagnosis

of alveolar-cell carcinoma was established by lobectomy; this patient had had a known exposure to a "sick" flock of sheep nine years before. Griffith, McDonald and Clagett[79] report 7 cases and note that the symptomatology offers little of diagnostic significance although cytologic examination of the sputum may show characteristic cells. Others have described profuse watery sputum as a highly suggestive complaint.

Cytologic examination of the sputum continues to be most useful in the diagnosis of pulmonary carcinoma.[80, 81] In a volume presented by the Vincent Memorial Hospital[82] on the subject of the cytologic diagnosis of cancer in general, the following statement is made:

> It has been our experience that smears of sputum and bronchial secretions present a more decisive picture than is true in other secretions. Cells which cause difficulty in interpretation are infrequent and these can be classified with fair assurance after experience.

In their hands sputum examinations have been consistently more satisfactory than bronchial secretions obtained during bronchoscopy.

Because the surgical treatment of cancer of the lung is still reserved for less than a majority of patients suffering from this disease, it is worth while to consider alternative forms of therapy. In this connection, the paper of Brooks and his co-workers[83] is of great importance. These authors report the experience of the Joint Consultation Clinic for Neoplastic Diseases of the Brompton Hospital and the Royal Cancer Hospital for the years 1944 through 1949. To this clinic were referred patients for radiation or chemotherapy, presumably when resection had been considered impractical or impossible. There were 502 patients in whom the diagnosis of bronchogenic carcinoma was accepted, with histologic confirmation in 306 and good clinical evidence in 196. The authors conclude that the palliative value of radiation is established, particularly in the relief of cough, hemoptysis and obstruction of the superior vena cava. It is not so useful for pain and in the presence of marked infection. Lynch, Ware and Gaensler,[84] on the other hand, find that the palliative gain from radiation therapy is not generally satisfactory or so effective as nitrogen mustard therapy. They report moderate to excellent subjective improvement for a short time in 69 per cent of 60 patients undergoing this form of treatment. The therapy, however, did not appear to offer significant prolongation of life. Only 13 per cent of their patients experienced severe nausea and vomiting, and 17 per cent showed a real leukopenia.

Radioactive materials have been introduced into the management of intractable pleural effusions that result from carcinomatosis of the pleura. Kent and Moses[85] report their use of I^{131}, Au^{198} and I^{131}-tagged human albumin in 19 cases. The method appears to have real usefulness in certain patients, sparing them the discomfort of rapidly recurring effusions.

In an effort to extend the bounds of operability, particularly when tumor involves the trachea, a great deal of experimental work has been done in the reconstruction of the trachea and major bronchi. Much of this has been the work of Gebauer,[86-88] whose primary objective has been the salvage of lung distal to healed tuberculous stenosis of the bronchus or trachea. He has demonstrated beyond doubt the usefulness of dermal grafts reinforced by fine wire, a technic that is particularly applicable where a window defect in the trachea has resulted from resection of a localized benign tumor. Where a complete circular defect has been created, the problem is more difficult. Many methods, including the use of preserved grafts, have been tested in the laboratory, and occasional operative cases in human beings are reported.[89-99] The subject has been well reviewed by Belsey,[100] and on the experimental side by Ferguson, Wild and Wangensteen.[101] The most recent report is that of Cotton and Penido,[102] who describe 2 cases of primary carcinoma of the intrathoracic trachea in which success followed complete circumferential resection of the trachea and reconstruction with a stainless steel tube.

(To be concluded)

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MEDICAL INTELLIGENCE

SOME CLINICAL AND LABORATORY OBSERVATIONS ON THE HYDRIODIDE OF DIETHYLAMINOETHYL ESTER OF PENICILLIN G (NEO-PENIL)*

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BOSTON

IN 1950, Jensen, Dragsted and Kiaer,[1] in Denmark, prepared the diethylaminoethyl ester of penicillin G and noted that it produced high levels in lungs and sputum after parenteral injection. Subsequently, they [2,3] showed that the hydriodide of this ester acted as a repository penicillin and also produced higher levels of penicillin in the lungs than either procaine penicillin or aqueous penicillin G (sodium salt). Clinical results in 13 cases of chronic bronchopulmonary infections and in 25 cases of pneumonia were highly favorable, the effects being exerted on penicillin-sensitive organisms.[4] These results were confirmed in Great Britain by Heathcote and Nassau[5] and by Matthews and Durie,[6] although the latter did not consider their clinical results superior to those obtainable with aqueous penicillin. In animals the new ester was found to show selective concentration, particularly in inflamed lung.[7] This ester was also found to be more effective in acute otitis media than procaine penicillin and as effective as "dipenicillin" (a mixture of aqueous sodium and procaine penicillin G) in such cases.[8] Blood levels were found to be lower and less prolonged than after similar amounts of procaine penicillin, but the plasma levels could be enhanced after intramuscular injection of "Neo-Penil"¶ by oral administration of Benemid.[9]

Because selective concentration and excretion by specific organs, particularly in inflamed tissues, may be a highly desirable property of effective antibiotics, further confirmation and clinical trials were considered warranted. A limited study of the clinical effects of Neo-Penil, primarily in acute and chronic bronchopulmonary infections and with particular reference to the penicillin levels obtainable in blood and sputum, was therefore undertaken. The results are presented in this paper.

MATERIALS AND METHODS

Patients

Neo-Penil was given to 42 patients on the Medical Wards of the Boston City Hospital; they ranged in age from twenty-eight to eighty years, and nearly two thirds of them were over fifty years old. Half the patients had acute pneumonia; of these cases, 13 were due to pneumococci, including 1 with bacteremia; the others were associated with other common respiratory pathogens — staphylococci, streptococci, *Haemophilus influenzae* and, in 1 case, *Klebsiella pneumoniae*. Most of the remaining patients had chronic nontuberculous bronchopulmonary infections, usually with acute exacerbations at the time treatment was instituted; only 1, however, had an acute lung abscess. There were 6 patients to whom Neo-Penil was given primarily for nonpulmonary infections to obtain penicillin levels in various body fluids; 3 of them had purulent arthritis (1 pneumococcal and 2 gonococcal), 2 had pleurisy with effusion, and 1 had ascites. Several patients with pulmonary infections received procaine penicillin, or aqueous potassium penicillin G before or after the Neo-Penil (or both) to compare sputum and blood levels with the different agents. In a few cases other antibiotics or sulfonamides, or both, were given when penicillin-resistant organisms replaced the sensitive ones in the sputum.

Penicillin Levels

The concentrations of penicillin in citrated plasma and in sputum were determined by a modification of

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¶"Neo-Penil" is the trade name adopted by Smith, Kline and French Laboratories, Philadelphia, for the hydriodide of diethylaminoethyl ester of penicillin G. We are grateful to their Medical Department for a generous supply of this product.

the *Sarcina lutea* cup-plate method[10] utilizing 12.7 mm. filter-paper disks (Schleicher and Schuell, No. 740E) instead of cups. Freshly raised samples of sputum were collected in sterile Petri plates at the time when blood was drawn; the patient rinsed the mouth and throat with water before producing the sputum samples, some of which were also used for cultures. The disks were saturated with the test material, usually undiluted, and then gently blotted between two sheets of filter paper ("Bilirubin Test Paper," Schleicher and Schuell, No. 470W) before being placed on the seeded agar plates. Penicillin concentrations are expressed in micrograms per cubic centimeter. (1 microgram = 1.6 units.)

Dosage

With few exceptions Neo-Penil was given in doses of 500,000 units suspended in 1.5 cc. of distilled water every twelve hours. The total dose per patient varied from 3 to 25 gm. given over a period of two to twelve days except for 4 patients who received smaller amounts for the primary purpose of obtaining body fluids for assay and 1 patient who received 72 gm. in seven weeks. Otherwise, the average dose per patient was 10 gm. given in ten days. Procaine penicillin was also given in aqueous suspension, and potassium penicillin G was given in aqueous solution in similar total volumes for the individual injections. All these agents were given intramuscularly.

Results

Concentrations of Penicillin in Plasma and Sputum

The levels of penicillin in blood and sputum of patients receiving an aqueous suspension of Neo-Penil in doses of 500,000 units every twelve hours are charted in the left panel of Figure 1; both the values for the individual specimens and the mean values for specimens obtained at various intervals after a dose are given. These samples were obtained after the patients had been receiving Neo-Penil for varying periods, usually three days or longer. For comparison, the results of a few observations in patients receiving an aqueous suspension of procaine penicillin in similar doses are shown in the central panel, and some in patients receiving different doses of a solution of potassium penicillin are presented in

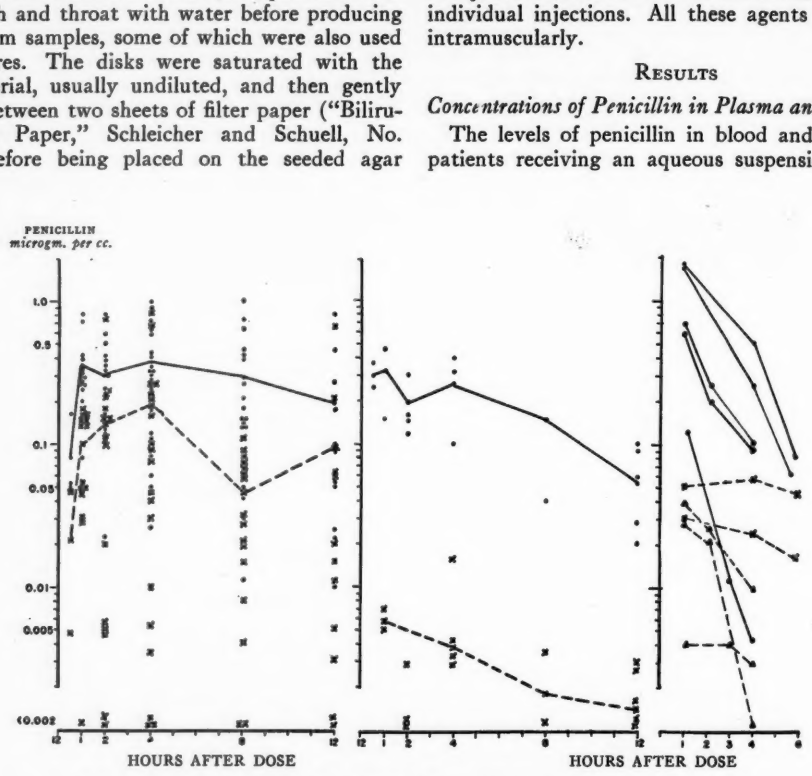

FIGURE 1. *Concentrations of Penicillin in Plasma (Dots) and Sputum (Crosses).*
Left = concentrations during treatment with Neo-Penil, 500,000 units intramuscularly in aqueous suspension every twelve hours. (Solid line connects mean values for plasma, and broken line connects mean values for sputum.)
Center = concentrations during treatment with 500,000 units of procaine penicillin in aqueous suspension intramuscularly every twelve hours. (Solid line connects the mean values for plasma, and broken line those for sputum.)
Right = concentrations of penicillin during treatment with aqueous potassium penicillin G. The solid lines connect values for plasma, and the broken ones for sputum of individual patients. The upper two solid and broken lines are from patients receiving 250,000 units every six hours, the others are from patients receiving 100,000 units every four hours.

the right panel of the same figure. It is seen that although there was considerable variation in individual specimens, the highest levels for sputum were obtained during Neo-Penil administration. The highest ratio of sputum to plasma levels, as indicated in this chart by the closer approximation of the sputum levels to those in plasma, was also obtained in the patients treated with Neo-Penil.

Comparisons of results obtained in a patient who received both Neo-Penil and procaine penicillin with those in another, who was given Neo-Penil and potassium penicillin, are shown in Figure 2. In these patients the different agents had been given in succession, and the specimens were obtained for assay after the patients had received the indicated agent and dosage for several days and for not less than five days. The strikingly higher levels in the sputum of both these patients during Neo-Penil administration and the higher ratios of sputum to plasma levels while they were receiving the new penicillin ester are clearly shown in each case.

The results of assays for penicillin in various body fluids and in exudates other than expectorated sputum are listed in Table 1. The ratio of the concentrations of penicillin in these body fluids to those found at the same time in plasma were quite high, being comparable and probably greater than those previously encountered under similar circumstances in patients receiving aqueous penicillin salts or procaine penicillin. However, direct comparisons in the same patients under different forms of therapy were not made.

Clinical and Bacteriologic Effects

Since controlled studies in patients treated with other forms of penicillin or with other antibiotics were not carried out in parallel, and since the total number of cases treated with Neo-Penil was small, the clinical results are presented only qualitatively and briefly. The clinical response to Neo-Penil, 500,000 units every twelve hours (and in 2 cases once daily) in the patients with acute pneumonia due to penicillin-sensitive organisms was in every way comparable to those generally seen in similar patients receiving aqueous salts of penicillin in doses of 100,000 to 250,000 units every three or four hours. In the pneumococcal pneumonias the temperature began to drop within twelve to twenty-four hours of the first injection of Neo-Penil and reached normal in each case within twenty-four to seventy-two hours. Acute symptoms cleared rapidly along with the fever; pulmonary signs began to improve simultaneously, with clearing after varying intervals as with other forms of effective antimicrobial therapy. Some of the pneumonias associated with other organisms improved in a similar manner; others responded somewhat less promptly.

Pneumococci cleared promptly, and penicillin-sensitive streptococci and staphylococci more slowly. In several patients *H. influenzae* also cleared along with other sensitive strains, whereas in some cases this organism persisted in spite of the fact that the patients continued to improve clinically. In 1, however, the persistence of *H. influenzae* in the sputum in large numbers was associated with failure of the patient to improve under Neo-Penil therapy; treatment with aureomycin resulted in rapid clinical cure, with clearing of *H. influenzae* from the sputum. In another patient, *K. pneumoniae* were found in abundance on the second day of Neo-Penil therapy when the patient was still acutely ill; administration of streptomycin was then followed by rapid improvement.

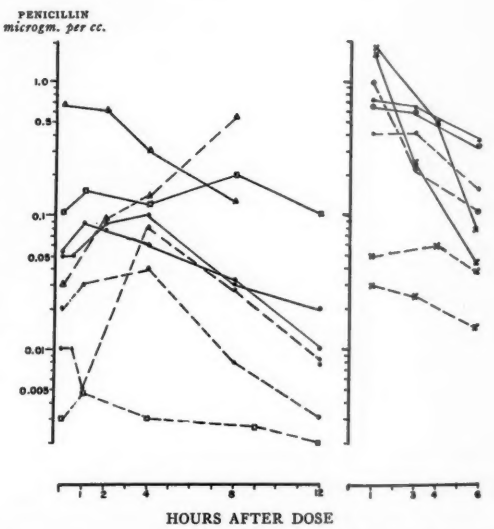

FIGURE 2. *Penicillin Levels in Plasma (Solid Lines) and Sputum (Broken Lines) during Different Forms of Therapy in 2 Patients.*

Left = patient P. C. who received Neo-Penil, 500,000 units every twelve hours (dots), Neo-Penil, 500,000 units every eight hours (open triangles) and procaine penicillin, 500,000 units every twelve hours (open squares).

Right = patient H. C., who received Neo-Penil, 500,000 units every twelve hours (dots), Neo-Penil, 250,000 units every six hours (open circles) and aqueous potassium penicillin, 250,000 units every six hours (crosses).

In the cases of chronic bronchopulmonary infections, the immediate effects were uniformly favorable in patients who had fever and symptoms of acute exacerbations. The effect on the chronic suppurative process was also generally favorable. Fever subsided more gradually in these patients. The volume of sputum decreased rapidly in almost all, and the sputum changed from thick and purulent to mucoid and much less purulent. In a few patients whose sputum had a foul odor, this odor cleared promptly after Neo-Penil treatment was in-

stituted. The patients' appetites improved, as did the general condition, and some who were undernourished began to gain weight. A large lung abscess in 1 patient decreased gradually in size during several weeks of therapy with penicillin — Neo-Penil was used alone for the most part, but other forms were employed part of the time in this patient for comparative studies of penicillin levels.

There were 2 apparent failures. In 1, low-grade fever persisted after an initially favorable response, and the patient was demonstrated to have active tuberculosis. The other patient had long-standing disease, with marked emphysema and cor pulmonale; his condition was not improved with Neo-Penil, nor did he subsequently benefit appreciably from other antimicrobial therapies.

In all these cases the penicillin-sensitive organisms cleared rapidly. In some, however, the flora in the sputum was replaced by resistant staphylococci, *Streptococcus viridans* and gram-negative bacilli without exacerbations of symptoms in most cases. In 3 patients therapy with aureomycin or terramycin was given in an attempt to clear a residual low-grade fever associated with the presence of a penicillin-resistant flora.

In the patients with purulent arthritis, the exudate became sterile promptly. The first synovial fluid obtained twelve to thirty-six hours after the beginning of Neo-Penil therapy was sterile on culture, and organisms could no longer be seen in stained smears of these exudates. Penicillin appeared promptly and in significant concentrations in synovial and other body fluids after single or multiple doses of Neo-Penil (Table 1).

Table 1. *Concentrations of Penicillin in Plasma and Other Body Fluids Obtained Simultaneously After Intramuscular Injections of Neo-Penil.*

Subject	Interval After Dose	Dosage*	Body Fluid	Concentration of Penicillin		
				in fluid	in plasma	ratio of fluid to plasma
	hr.	*units*		*microgm./cc.*	*microgm./cc.*	*microgm./cc.*
H. B.	3	500,000	Bronchial secretion†	0.01	0.16	0.06
C. B.	2	500,000‡	Bronchial secretion†	0.06	0.25	0.24
D. C.	4½	500,000‡	Bronchial secretion†	0.02	0.09	0.22
F. W.	1	500,000‡	Bronchial secretion†	0.05	0.23	0.22
J. H.	4	500,000	Pleural fluid	0.27	0.80	0.34
J. H.	4	1,000,000	Pleural fluid	0.35	0.19	1.8
J. K.	4½	500,000	Pleural fluid	0.30	0.11	2.7
P. N.	2	500,000‡	Pleural fluid	0.10	0.37	0.27
D. G.	7	500,000§	Synovial fluid	0.01	0.01	1.0
W. M.	6	500,000‡	Synovial fluid	0.50	0.60	0.83
W. M.	1	500,000‡	Synovial fluid	0.22	0.14	1.6
*E. H.	1½	500,000	Spinal fluid	0.04		
T. R.	6	500,000§	Ascitic fluid	0.27	0.29	0.93

*Single dose unless otherwise noted.
†Bronchial secretions obtained through bronchoscopic aspiration.
‡Every 12 hours.
§Every 8 hours.

Toxicity

The first preparations of Neo-Penil made available to us produced considerable local pain and tenderness; all subsequent lots to date, however, have been almost entirely free of local reactions. Indeed, the injections of Neo-Penil in the doses used have been better tolerated than those of similar amounts of solutions of potassium or sodium penicillin in the same patients. In 2 cases urticaria developed, in 1 on the twelfth day after treatment was begun and two days after the last dose of Neo-Penil and in the other on the fifteenth day of continuous therapy. Both patients had received 500,000 units intramuscularly every twelve hours, and neither had previously received any penicillin. In both cases the symptoms were alleviated by antihistaminics and local antipruritic agents.

No other untoward effects from Neo-Penil were noted in any of the 42 patients observed in this study. Wylie-Smith,[11] however, reported an anaphylactic shock-like reaction with convulsive movements and unconsciousness that promptly followed an intramuscular injection of the diethylaminoethyl ester hydriodide. Heathcote and Nassau[6] obtained no untoward effect from the compound, but after injection of the hydrochloride of the ester (which is more soluble and more rapidly absorbed) they observed bronchial spasm in 1 patient and a syncopal attack in another. Similar reactions, including anaphylactic shock, convulsions and syncope, have been reported after injections of procaine-penicillin[12-14] and even after aqueous crystalline penicillin.[15] Most of these reactions were probably allergic, but those following the injections of the poorly soluble esters may have represented the effects of accidental intravenous injections.

Summary and Conclusions

The hydriodide of diethylaminoethyl ester of penicillin G (Neo-Penil) in aqueous suspension is a repository preparation of penicillin. Significant concentrations of penicillin appear in sputum and other body fluids after intramuscular injection of

Neo-Penil. The concentrations of penicillin in sputum and the ratio of these concentrations to those found in the plasma are higher after Neo-Penil than after similar amounts of aqueous suspensions of procaine penicillin or solutions of potassium penicillin G. Clinical and bacteriologic effects of Neo-Penil therapy in a small number of patients with acute pneumonia and chronic bronchopulmonary infections were favorable. Although these data are insufficient to indicate any superiority of Neo-Penil over procaine penicillin or the soluble salts of penicillin G, the higher concentrations of penicillin in sputum during Neo-Penil therapy and the fact that intramuscular injections of Neo-Penil appear to be better tolerated than other forms of penicillin suggest that it deserves further trial in bronchopulmonary infections due to penicillin-susceptible organisms.

We are indebted to Miss Marilyn Broderick and Miss Clare Wilcox for technical assistance and to the members of the hospital staff for their co-operation.

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SWIMMER'S MUSCLE CRAMPS

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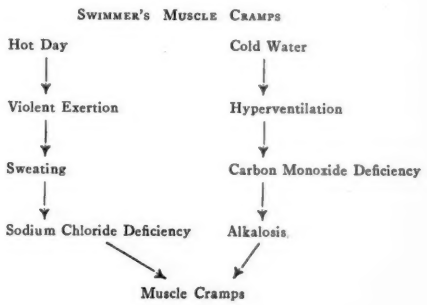
As a young physician, I was sternly taught never to submit any paper for publication that contained theory unsubstantiated by fact. Now that I have reached a riper age — indeed, one that approaches medical senility — I am wondering if the *Journal's* new section entitled "Medical Intelligence" may not offer me an outlet for some of those wonderful theories I was never able, or was ever too lazy, to substantiate by experiment.

At any rate, here goes:



Possibly, after all, there was something in the old admonition not to go swimming after violent exercise. Perhaps many a healthy young man — or not so healthy old one, for that matter — would have spared his life by adhering to one of the following rules, or preferably both: after exercise on a hot day either wait until plenty of salty fluid has been assimilated or do not swim beyond your depth unless someone with a handy boat (and one who knows how to use it) is watching you.

I am quite sure that the advice is good, even if the theory is not.

*Member, Board of Consultation, Massachusetts General Hospital.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 38471

PRESENTATION OF CASE

First admission. A sixty-four-year-old woman was admitted to the hospital because of anorexia and pain in the lumbar region.

Three years before admission, at another hospital, the patient had had a left radical mastectomy for carcinoma of the breast, two out of four lymph nodes being found positive for metastatic tumor. Eleven months before admission a single nodule of recurrent tumor was excised from the anterior axillary line. Two months later sodium estrone sulfate, 30 mg. daily, was begun because of pulmonary metastases diagnosed by x-ray examination. At this time she was said to have had phlebitis with a swollen left leg. She remained asymptomatic although an increase in the pulmonary lesions was noted in the x-ray film taken five months prior to admission. There was questionable slight improvement of the pulmonary lesions two months before admission, at which time the hormone therapy was stopped. Over the five months prior to admission her weight had fallen from 145 to 123 pounds. The patient had attributed the onset of her anorexia to the institution of estrogen therapy, but she had noted no improvement upon its withdrawal. Five weeks before admission pain developed in the lumbar area and was severe enough to confine her to bed.

On physical examination the heart and lungs were normal. The right breast was normal, and no nodules were palpable in the mastectomy scar. The liver was not felt.

The temperature was 97.2°F., the pulse 72, and the respirations 22. The blood pressure was 136 systolic, 72 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 13.4 gm. per 100 cc. and a white-cell count of 8900. The total protein, albumin-globulin ratio, calcium, phosphorus, alkaline phosphatase and nonprotein nitrogen were within normal limits. The vital capacity was 1.6 liters. The basal metabolic rate was +4 per cent. X-ray examination showed an irregular density in the upper halves of both lung fields that had a strand-like and mottled character. There was some loss of volume of both upper lobes. The trachea and esophagus were displaced markedly to the right in the lower portion of the neck and for a short distance substernally by a soft-tissue mass that moved upward with swallowing and demonstrated no intrinsic calcification. Films of the thoracolumbar spine and skull failed to disclose any definite metastatic lesions although there were several small suspicious areas in the left iliac wing. A gastrointestinal series was unremarkable.

The patient was discharged improved on the tenth hospital day.

Second admission (seven months later). In the interval the anorexia had decreased, and the patient had begun to gain weight. Six weeks prior to admission she began to lose appetite, weight and strength. During the few days before entry vomiting and fever had developed.

Physical examination revealed no significant changes.

The temperature was 98.4°F., the pulse 92, and the respirations 24. The blood pressure was 110 systolic, 70 diastolic.

The urine had a specific gravity of 1.016 and gave a + test for albumin; the sediment contained 5 red cells, 10 white cells and occasional coarsely granular and finely granular casts per high-power field. Examination of the blood showed a hemoglobin of 10.2 gm. per 100 cc. and a white-cell count of 9800, with a normal differential. The eosinophil count was 200 per cubic millimeter. The serum sodium was 119.2 milliequiv., the chloride 94 milliequiv., and the potassium 4.1 milliequiv. per liter; the nonprotein nitrogen was 15 mg., the alkaline phosphatase 4 units and the fasting blood sugar 84 mg. per 100 cc. The total protein and albumin-globulin ratio were within normal limits. Sputum culture gave a moderate growth of *Staphylococcus aureus* and abundant alpha-hemolytic streptococci, and sputum smears were negative for tubercle bacilli. The x-ray films showed further infiltrative change in both lungs, principally in their upper halves, but also extending to involve the lower portions of both lungs (Fig. 1). A gastrointestinal series was again unremarkable.

The patient was given transfusions, vitamin supplements intravenously and fluid, with some improvement in her electrolyte balance. She had episodes of severe depression, which she had had for several years. She continued to be very weak, with vomiting, diarrhea and a low serum sodium. On the twenty-first hospital day the temperature spiked to 105°F. Physical examination at this time revealed the presence of bronchial breathing and fine rales in the left side of the chest. No skin pigmentation was noted. The heart was small on

percussion; the blood pressure was 85 systolic, 50 diastolic, and the pulse was 120. The blood sodium was 152.9 milliequiv. per liter; the other laboratory data were normal. On the following day cortisone therapy was begun in a dosage of 50 mg. by mouth daily for four days and 25 mg. thereafter, as well as Crystacillin, 300,000 units, and streptomycin, 0.5 gm. daily. X-ray films on the thirty-fifth hospital day showed a radiolucent zone in the contracted left apical segment measuring 1.5 by 2 cm. and surrounded by a wall 3 to 4 mm. in thickness. The patient improved on this regimen and was discharged on the forty-second hospital day.

Final admission (eight days later). After discharge she continued to take cortisone, streptomycin and multivitamin capsules. She felt well until three days prior to admission, when she noted abdominal bloating followed by epigastric soreness,

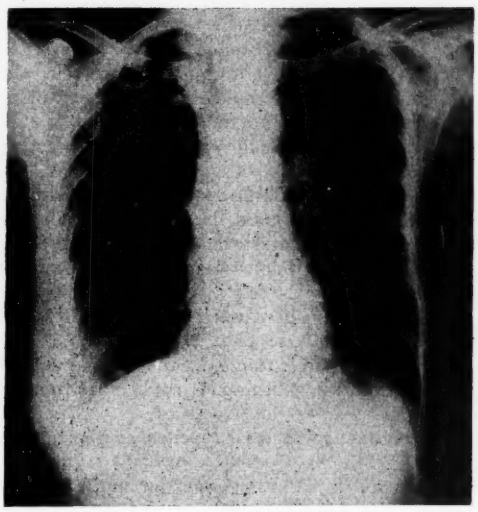

FIGURE 1. *Chest Film Two Months before Death, Showing Upper-Lobe Lesions and Displacement of the Trachea and Esophagus by the Enlarged Thyroid Gland.*

mild cramps, nausea, vomiting and weakness. There was much dyspnea when she climbed stairs.

Physical examination showed the chest to be clear, with amphoric breathing over the left upper lobe anteriorly. The heart size was normal. There was an almost imperceptible pulse of 88, which was regular with rare ectopic beats. The blood pressure, which was difficult to obtain, was not above 90 systolic, 70 diastolic. The abdomen was distended with gas, without a fluid wave. Peristalsis was present. The temperature was 97°F. by rectum.

Examination of the urine showed a specific gravity of 1.022 and a + test for albumin. The hemoglobin was 12.6 gm. per 100 cc., and the white-cell count 8900, with 49 per cent neutrophils, 45 per cent lymphocytes, 3 per cent monocytes and 3 per cent eosinophils. The serum sodium was 122.2 milliequiv., the chloride 90 milliequiv. and the potassium 5 milliequiv. per liter; the nonprotein nitrogen was 28 mg., and the blood sugar 107 mg. per 100 cc.

The patient was given large amounts of saline solution intravenously; the serum sodium, chloride and potassium were within normal limits on the third hospital day. However, she became edematous, anuric and weaker. During the last eight days in the hospital the urinary output ranged from 150 to 250 cc. She died quietly on the ninth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH W. GARDELLA*: When I first reviewed the protocol it seemed almost certain to me that the terminal events in this case were due to adrenal destruction by metastatic tumor. This diagnosis appears quite consistent with the course of the disease. About three and a half years after the discovery of metastatic tumor, signs and symptoms of marked adrenal failure developed over a period of about six weeks. Six weeks is a rather brief period for conditions like tuberculosis or primary atrophy to produce adrenal failure, and certainly it is too long for such things as hemorrhage or necrosis of the adrenal gland or thrombosis of the adrenal vessels. It is difficult to be certain that the onset of adrenal insufficiency was not more protracted, since the early symptoms of adrenal failure would have been indistinguishable from those provoked by the metastatic carcinoma. Yet, in the six months preceding the onset of adrenal insufficiency, hospital studies failed to reveal any signs of adrenal hypofunction, and after discharge her condition improved. This series of events suggests a subacute but progressively destructive process of the adrenal cortex, and in the presence of metastatic disease the most likely diagnosis is replacement and destruction of the adrenal gland by secondary tumor. In support of this possibility one finds from Willis[1] and other sources that the adrenal glands are involved in 20 per cent of the cases of metastatic carcinoma of the breast. Moreover, these metastases are characteristically extensive and bilateral.

I was able to find no serious objection to this diagnosis until I uncovered the disquieting information that evidence of marked adrenal insufficiency, even in cases with grossly complete destruction of both glands, is exceedingly rare. Apparently, considerable amounts of functioning cortical tissue can usually be found microscopically, even in cases in which grossly the adrenal glands appear to be completely replaced by secondary tumor. This information was a severe blow to my thesis. I found it difficult to accept so I scanned the litera-

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ture since the time of Addison and uncovered about 12 cases of secondary adrenal tumor reported in association with adrenal insufficiency. However, the cases I was able to review were poorly documented, and the authors seemed to have had difficulty in distinguishing the early signs of adrenal failure from the late signs of metastatic disease. Yet a case reported by Strang[2] described extensive metastases to the adrenal glands from bronchogenic carcinoma with adrenal insufficiency that was well substantiated. Furthermore, Dr. George W. Thorn, whom I consulted about this, apparently has also seen such cases. The net result of my survey, therefore, seems to be that adrenal insufficiency resulting from destruction by secondary tumor may occur but is exceedingly rare. Yet, as rare as this combination may be, I find it difficult to abandon entirely. Nevertheless, its statistical improbability forces the consideration of other conditions that might be responsible for the presumed adrenal failure in this case.

I suppose it is possible that the adrenal insufficiency was secondary to a destructive process of the pituitary body consequent to metastatic tumor. Like those of the adrenal gland, secondary tumors of the pituitary body are not unusual with carcinoma of the breast. The metastases, however, are almost always confined to the posterior lobe, and diabetes insipidus is often manifest. Moreover, there was no other evidence of destruction of the anterior pituitary gland in this case: the basal metabolic rate was normal, and there were no neurologic or x-ray findings to suggest such a process. I do not find this possibility very exciting.

Overwhelming infection, toxemia or bacteremia with hemorrhage not infrequently causes adrenal failure, but these are explosive processes, and the manifestations of infection are rarely subtle. Other infectious diseases such as histoplasmosis and torulosis, with invasion and destruction of the adrenal glands, have been associated with adrenal insufficiency, but no other clinical manifestations of these diseases were present in this case.

Amyloid disease of the adrenal glands is not infrequent. Actually, in almost all cases of generalized amyloidosis, deposits are regularly found in the adrenal glands. But as with secondary tumor, destruction is rarely extensive enough to produce adrenal insufficiency.

Of the possibilities remaining, tuberculosis and primary atrophy of the gland seem most promising.

Before deciding about these I should like to see the x-ray films.

DR. JOSEPH HANELIN: Did this patient ever have irradiation of the lungs?

DR. RITA M. KELLEY: I do not believe so.

DR. HANELIN: The first film made nine months before death shows peculiar strand-like densities in the upper halves of the lungs and deviation of the trachea and esophagus to the right by the mass in the lower portion of the neck, which appears to extend a short distance into the mediastinum. The lower halves of the lungs are relatively free of disease. The appearance of these lesions and their distribution in both upper lobes are not typical of metastases, but rather suggest some infectious process. In films taken six, seven and eight months later there appears to be some progression of the lesions; particularly at the seven-month interval there appears to be definite evidence of spread of the process into the lower halves of the lungs (Fig. 1). About two weeks later there is some accumulation of fluid in the left side of the chest. There has been no striking change in the heart size.

DR. GARDELLA: Is the heart small?

DR. HANELIN: No.

DR. GARDELLA: The chest films taken in the second admission showed a radiolucent zone.

DR. HANELIN: I think this is the radiolucent area referred to. There was some question of cavitation in the left lung.

DR. GARDELLA: How much of a question?

DR. HANELIN: I do not think it is certain. In these films I cannot completely trace the wall of what was thought to be the cavity.

DR. GARDELLA: Would you call this infection or tumor?

DR. HANELIN: I should favor an infectious process rather than metastases, but I cannot rule out metastases. If it is metastatic disease, it is atypical.

DR. GARDELLA: There was some suggestion of bony metastases in the left iliac wing.

DR. HANELIN: There were several small radiolucent shadows in one film.

DR. GARDELLA: Nothing in the lumbar spine?

DR. HANELIN: Nothing I could interpret as metastasis.

DR. GARDELLA: What happened to the lumbar pain?

DR. PERRY J. CULVER: She did not have any after the second admission.

DR. GARDELLA: She came in the first time for the lumbar pain.

DR. HANELIN: There is some loss of height in the first lumbar vertebra that remained constant over the seven-month interval.

DR. GARDELLA: No evidence of calcified adrenal glands?

DR. HANELIN: No.

DR. GARDELLA: I am depending on your opinion to establish metastatic disease.

DR. HANELIN: When we first saw these films we had to say we could not indicate etiology. We were torn between an infectious lesion such as tuberculosis and rather peculiar distribution of metastases.

DR. WARREN W. POINT: During the last seven days in the hospital this woman had an absolutely unobtainable blood pressure by any means what-

soever, and the heart sounds were almost imperceptible; it was fantastic.

DR. GARDELLA: I don't know whether the picture you describe is inconsistent with terminal adrenal failure. I can think of no other explanation unless a massive vascular accident within the abdominal cavity complicated the picture.

I had hoped to obtain some help in differentiating neoplasm from tuberculosis on the chest films. Since this seems impossible, I am forced to rely upon the history of the onset of adrenal insufficiency to make this differentiation. If adrenal failure had occurred more insidiously, I would suspect tuberculosis rather than neoplasm. Yet the evidence indicates that the adrenal failure occurred no earlier than a few weeks before death. The blood pressure at the time of the second admission was normal, and no other signs of adrenal hypofunction were noted. The absence of pigmentation also suggests that this was not Addison's disease due to tuberculosis or primary atrophy. I think, however, that the clinicians were concerned with the possibility of tuberculosis, and this disturbs me.

The tracheal and esophageal displacement I am not able to fit into the picture. The mass in the neck moved with swallowing so there was apparently no infiltration of the peritracheal lymph nodes with tuberculosis or cancer. The thyroid gland was not hard. Perhaps the mass was nothing more than an enlarged goiter.

Before this meeting I believed this patient had metastatic disease of the adrenal glands, with resultant adrenal insufficiency. I do not see how I can retreat at this point. Statistically, it is an improbable diagnosis, but it seems to me the most logical. For the sake of statistics, I shall throw in hemorrhage within or vascular thrombosis of the adrenal glands. I assume that there was metastatic disease of the lungs. She may have had metastases in the liver that contributed to the gastrointestinal symptoms in part, and possibly in the bones to account for the back pain. Whether the thyroid gland contained metastases, it is difficult to say. The mass in the neck was soft and not characteristic of tumor.

Dr. Point, is it true that there was a rather acute change in the terminal picture?

DR. POINT: Yes; the patient did not respond to epinephrine given as an intravenous drip over a twelve-hour period. The blood pressure did not rise.

DR. GARDELLA: The only explanation I have is mesenteric thrombosis of an intra-abdominal vein with perhaps thrombosis of an adrenal vessel. The picture does not seem to have been due to cardiac failure since the heart size was reported to be normal. The respiratory symptoms seem to have been due to a compromise of pulmonary function.

Before closing I should consider briefly other conditions that may simulate adrenal insufficiency. The vomiting and diarrhea were slight and, I am sure, contributed little to the electrolyte loss.

Could primary renal disease such as the "salt-losing" nephritis described by Thorn[3] be mistaken for adrenal insufficiency? There were formed elements in the urine on one occasion, but the presence of an adequate degree of urine concentration and a small amount of nitrogen retention mitigate against a diagnosis of diffuse renal disease as is seen in "salt-losing" nephritis. The patient may have had a mild degree of pyelonephritis but hardly severe enough to account for the serious electrolyte loss. Secondary tumors of the kidneys from cancer of the breast do occur but are rarely, if ever, associated with renal insufficiency. Thus, I find myself somewhat intolerant of possibilities other than adrenal failure to explain the course of the terminal events in this case.

DR. KELLEY: I saw the patient on the first admission after these films were interpreted as showing metastatic disease and she was placed on hormones. I should like to point out that the second admission was not for back pain primarily but for malnutrition. She attributed her loss of appetite and weight to the hormones she was getting. When the possibility of infection was raised, the hormone was withdrawn. The main problem throughout the admission continued to be one of absolute refusal to eat, with profound malnutrition and the typical signs of vitamin deficiency. The back pain was a minor problem and was not the concern of the major part of the therapy.

DR. DONALD S. KING: The high fever and the symptoms of Addison's disease I thought could best be explained by tuberculosis. One of the interesting things was the therapeutic problem; if this was tuberculosis, should she have been given ACTH and cortisone? ACTH and cortisone may reactivate an old tuberculous process. We believed that the evidence for active tuberculosis was not sufficient definitely to contraindicate the use of ACTH because of the apparent beneficial effects in this particular case.

DR. JACOB LERMAN: As I recall, studies [4, 5] have indicated that changes in sodium, chloride and potassium, simulating Addison's disease, may occur in pulmonary infections (tuberculous or nontuberculous). The absence of pigmentation makes one believe that this is an example of pulmonary infection with the laboratory findings of Addison's disease without the actual Addisonian picture.

DR. CULVER: We were somewhat slow in recognizing the adrenal insufficiency because the initial anorexia was thought to be psychogenic. A psychiatrist even went so far as to postulate that this patient might have seen cases of metastases and terminal carcinoma, and did not eat on that basis. It was thought that her illness all went back to a

depression. Immediately prior to the time the adrenal insufficiency was recognized, there was a discussion about admitting her to a mental hospital for electric-shock therapy.

DR. POINT: One more consideration that seemed to point toward tuberculosis was the fact that the belly was extremely doughy. On the last admission she was given adequate quantities of adrenocortical extract to the point that the electrolytes became normal. The blood pressure remained unobtainable.

DR. ANNE FORBES: I should like to ask whether it is unusual to have so little progression in a metastatic lesion? She was ill for twelve months.

DR. BENJAMIN CASTLEMAN: It is not unusual with metastases from carcinoma of the breast; they may grow very slowly and frequently stimulate connective tissue. I have even seen such lesions appear smaller on the x-ray films after hormone treatment.

CLINICAL DIAGNOSES

Adrenal insufficiency.
Tuberculosis, pulmonary and peritoneal.

DR. GARDELLA'S DIAGNOSES

(Carcinoma, left breast), with metastases to adrenal glands, lungs and ? bones.
Adrenal insufficiency.
Hemorrhage or vascular thrombosis of adrenal glands.

ANATOMICAL DIAGNOSES

(Carcinoma, left breast), with metastases to lung, bones, liver, gall bladder, omentum, pituitary body and pericardium.
Hemopericardium, with cardiac tamponade.
Adrenal atrophy secondary to metastatic carcinoma in pituitary body.
Pulmonary emboli and infarction.
Hydrothorax, bilateral.
Colloid goiter.
Operation: radical mastectomy, left (four years).

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy explained the lack of blood pressure for seven days. The heart was very small, weighing only 200 gm., and lay in a pericardial cavity containing 600 cc. of old and recent blood. The cause of the hemopericardium was a small metastasis, under 1 cm. in diameter, at the base of the heart on the inner aspect of the parietal pericardium, which was surrounded by a great deal of old blood. There was one other smaller similar lesion but no other metastases to the pericardium. I believe there had been a slow oozing of blood from erosion of a vessel by the metastasis that gradually developed into a tamponade. Unfortunately, the patient was too sick for a chest film to be taken in the last admission. The lesions in the lungs were limited to the upper thirds of the upper lobes and were all due to carcinoma with fibrosis. There were broad areas of fibrosis without any real necrosis at the time of autopsy. Nothing suggested tuberculosis. We were unable to find the cavity suspected in the x-ray films, although we looked very carefully for it.

In the vertebral column there were 6 or 7 vertebras that were almost completely replaced with a dense, fibrous type of carcinoma. The stroma elaborated by the carcinoma was great. There were a few small metastases in the liver, but by and large the patient did not have very much metastatic disease in the other organs of the body.

The adrenal glands were quite interesting. They were atrophic; one weighed 2.5 gm. and the other under 3 gm., which is less than half the normal weight. The atrophy was primarily in the cortex. We found two small islands of metastatic carcinoma in the adrenal medulla. The cause of the atrophy of the adrenal glands was found in the pituitary body.

The entire pituitary gland — anterior and posterior lobes — was completely replaced by carcinoma. We do not understand why the patient did not have more signs of a panhypopituitarism. We made almost serial sections and could not find much pituitary tissue left. Here too the tumor had stimulated a great deal of connective tissue. The sella turcica was also completely replaced by carcinoma. I believe this is one of the rare cases of destruction of the anterior pituitary body producing cortical atrophy of the adrenal gland. The ovaries were small and atrophic. The endometrium was also completely atrophic — very little stroma, and only one or two small glands. I suppose that may also have been due to the lack of hormones from the pituitary body. Were there any signs of panhypopituitarism?

DR. CULVER: There were no other signs. The pubic hair was quite normal.

DR. FORBES: The presence of axillary and pubic hair is consistent with recent panhypopituitarism. It takes several months for the effect of the hormones that cause the growth of axillary hair to wear off, and it takes further time after new hair has stopped growing for old hair to fall out.

The serum sodium level of 152 milliequiv. per liter is surprising if the patient's dehydration is to be ascribed to adrenal insufficiency. Such a high level in a conscious patient suggests pituitary insufficiency and fits in with the anatomic findings. There was no mention of increased thirst. However, I note from the patient's chart that the urinary output was equal to the fluid intake, even when this was 6 liters. The only recorded urinary specific gravity, however, was 1.022, which is against diabetes insipidus.

DR. GARDELLA: I had assumed that the high level of serum sodium was due to the overenthusiastic intravenous administration of saline solution.

DR. CASTLEMAN: The mass in the neck was a colloid goiter, which weighed 75 gm.

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CASE 38472

PRESENTATION OF CASE

A seventy-four-year-old former printer was admitted to the hospital because of abdominal swelling of three weeks' duration.

The patient had had for forty to fifty years bouts of epigastric soreness occurring about two hours after eating and relieved by bicarbonate of soda. Periods in which he had minimal or no symptoms alternated with more severe episodes, although at no time did symptoms prevent him from working. Ten months before admission he had a relatively more severe episode of nonradiating epigastric soreness associated with cramps in the middle and lower portions of the abdomen; however, after he had remained on a diet of ginger ale for three or four days, the symptoms subsided. Two months before admission severe cramps in the lower abdomen lasting one day developed, and at this time his physician found some epigastric tenderness, but the abdomen was flat. A roentgenogram was said to have shown "old inactive duodenal ulcers." At about this time the patient passed a stool that was darker than usual but not tarry. He was given tincture of belladonna, and again the symptoms subsided although a residuum of soreness remained. Six weeks before entry he had diarrhea for one day, with a total of four or five bowel movements, successfully treated with Kaopectate. The stools had been softer than normal since that time but were brown, and of normal volume; the bowel movements were regular. Approximately three weeks prior to entry he noted overnight swelling of the abdomen chiefly in the upper part. Ingestion of food was followed by generalized crampy abdominal pain, most severe in the upper portion. Since that time he had taken only soft-boiled eggs and milk in small quantities. He noted progressive weakness and exertional dyspnea, and lost 18 pounds in weight in the four weeks before admission. Bowel movements continued to be regular despite reduced food intake.

There was no history of nausea, vomiting, jaundice, intolerance to fatty foods, chills or fever. The patient took 1 or 2 quarts of ale daily in the few months before admission; in the past he had drunk several shots of whisky each day. He had had diphtheria at the age of ten and thirty-nine years and scarlet fever at the age of thirty-five.

Physical examination showed an alert, co-operative man with obvious signs of weight loss. The chest was emphysematous, and there were dullness and diminished breath sounds at the right base but no rales. The boundaries of the heart could not be easily percussed because of the emphysema, and the apical beat was not palpable. A Grade 1 systolic murmur was heard at the apex, and a Grade 2 systolic murmur over the aortic region. There was a normal sinus rhythm; the aortic second sound equaled the pulmonic. The abdomen was distended, most markedly in the upper abdomen; it was tympanitic throughout but more so over the distended portion, shading off into dullness in the flanks. There was shifting dullness but no fluid wave. No organs or masses were palpated. The prostate was enlarged, and there was + ankle edema.

The temperature was 102°F., the pulse 90, and the respirations 15. The blood pressure was 150 systolic, 84 diastolic.

The urine was light amber, had a specific gravity of 1.022, and gave a + reaction for albumin and a negative test for bile; the sediment contained 2 white cells per high-power field. Examination of the blood showed a hemoglobin of 9.8 gm. per 100 cc. and a white-cell count of 5000, with 70 per cent neutrophils, 26 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. The alkaline phosphatase was 3.6 units, the amylase 130 units, and the bilirubin 0.6 mg. direct and total per 100 cc.; the total protein was 4.94 gm., the albumin 3.11 gm., the globulin 1.83 gm. and the nonprotein nitrogen 29 mg. per 100 cc. The prothrombin time was 15 seconds (normal, 13 seconds) and the cephalin flocculation ++ in twenty-four and +++ in forty-eight hours. Three stool specimens were guaiac negative.

A roentgenogram of the chest was normal except for considerable elevation of the right side of the diaphragm, with absent movement on respiration and a small pleural reaction at the right base. On barium-swallow examination and gastrointestinal series no esophageal varices were seen. There was a hiatus hernia of the fundus of the stomach, which was small and high in position but otherwise normal. The duodenal cap was a little deformed but showed no definite ulcer. The duodenal loop did not appear unusual. A plain film of the abdomen revealed generalized increase in density and loss of detail of the posterior abdominal wall consistent with fluid, as well as a large soft-tissue shadow in the right side of the abdomen that was probably an enlarged liver (Fig. 1).

On the third hospital day abdominal paracentesis recovered 300 cc. of deep-green-yellow, viscid fluid that had a specific gravity of 1.015 and contained 1230 cells per cubic millimeter and no demonstrable tumor cells. A foam test on the fluid was positive

for bile. The fluid had a total protein of 3.6 gm. per 100 cc. and a bilirubin of 0.5 mg. direct, 3.6 mg. total, per 100 cc. On gastric aspiration 50 cc. of yellowish, bilelike fluid was removed. This had a pH of 7.5 and was negative to Töpfer's reagent. Cytologic examination of the gastric contents was reported as "positive."

On the fifth hospital day the total protein was 5.41 gm., the albumin 3.22 gm., the globulin 2.19 gm., the total bilirubin 0.7 mg., and the nonprotein nitrogen 42 mg. per 100 cc.; the sodium was 136.0 milliequiv., the chloride 100 milliequiv., and the carbon dioxide 25.9 milliequiv. per liter. The prothrombin time was 17 seconds (normal, 13 seconds). The urinary urobilinogen was 0.4 Ehrlich units in two hours. During this period of hospitalization, the patient continued to complain of cramps in the lower abdomen, and he had several episodes of cardiac arrhythmia treated with quinidine. Abdominal physical findings remained essentially unchanged, however, and he felt fairly well. The temperature ranged from 98.6 to 101°F. On the sixth hospital day the neck veins were slightly distended, and there were moist rales in the chest bilaterally. There was a definite fluid wave and ++ edema of the ankles and legs. The patient was digitalized, with disappearance of the neck-vein distention, rales and dyspnea. A barium-enema examination performed on the following day showed filling of the entire colon and appendix. The descending colon was displaced laterally, and the hepatic flexure was straightened and displaced medially and downward. No gross lesions were noted in the large bowel, and a post-evacuation film showed normal-appearing mucosa.

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FIGURE 1.

On the ninth hospital day peritoneoscopic examination revealed brownish-red, slightly thick fluid having a yellow foam. Inspection of the contents of the upper abdomen showed a great quantity of serofibrinous exudate obscuring the right lobe of the liver and overlying most of the viscera in the right upper quadrant. There was less exudate in the left upper quadrant. The left lobe of the liver, which was visualized, was partially covered by thin, transparent adhesions but was apparently free of tumor nodules. After the aspiration of 12 liters of this fluid, it was possible to see hundreds of tiny, punctate, papular nodules on the peritoneal surface of the anterior abdominal wall. It was impossible, however, to observe any in the upper quadrants because of the great amount of exudate. Throughout the procedure, the fluid aspirated became more and more bloody although the patient showed no sign of blood loss or shock. It appeared to the examiner that the bleeding was from diffuse oozing from peritoneal surfaces, especially in the upper quadrants and more on the right. No single site of bleeding could be identified. A biopsy of one of the peritoneal nodules was later reported as showing "chronic inflammation."

Upon his return from the operating room the patient was in shock, and during the next few days he went progressively downhill. Severe hiccuping developed, and for periods he was dyspneic, in shock and semicomatose. He complained of soreness in the lower abdomen but did not vomit and was not nauseated. The temperature curve was essentially as before, and the abdomen was soft, with some soreness on pressure over the lower portion, especially in the left lower quadrant.

There was a suggestion of a mass in the left upper quadrant close to the midline that moved on respiration. No other masses were palpated, and peristalsis was active. Fluid had reaccumulated since the peritoneoscopy.

On the twelfth hospital day the white-cell count was 30,000, with 94 per cent neutrophils, and the patient was comatose. Crystacillin, streptomycin and blood transfusions were administered, and on the following day the temperature and pulse had dropped to normal and the white-cell count to 12,000. A diagnostic abdominal tap was done, with the removal of 10 cc. of pink fluid that had a hematocrit of 2 per cent. Hypotension, labored respiration and coma persisted, however, and one day later the patient died.

Differential Diagnosis

Dr. John W. Raker*: This case is more than somewhat confusing. I do not think I can make a definite diagnosis on the evidence presented. Apparently, the physicians who cared for the patient in the hospital were also not certain of the diagnosis; they continued to carry out diagnostic procedures to the time of death. The main problem they must have faced was whether or not this man should be explored. They must have weighed the possibility of finding a surgically correctable lesion against the risk of operation in a critically sick patient. On the record alone I think the decision not to explore was wise.

I have two questions to answer, What was the location of the primary trouble, and What was its nature? I shall try to deal with the latter in a general way first. The process was probably either inflammatory or malignant; in a person of this age with a progressive course and progressive weight loss, I think a malignant process is strongly suggested.

Before discussing the location of the primary disease, I can exclude a diffuse systemic disease, such as Osler's disease, with purpura of that variety. Although I shall have trouble explaining the bleeding, I cannot find any other evidence of generalized systemic disease.

Congestive heart failure developed, at least once mildly and once more severely during the course of the illness. The patient had an arrhythmia, which was apparently quite severe. The ascites does not appear to have been due to the heart failure. I suppose he probably had a certain degree of coronary-artery disease, and he may have had calcareous aortic stenosis although the evidence for that is slim. I should think the cardiac condition was not the primary cause of the difficulties. He had disease in the lungs, — emphysema and pleural fluid, — but the pleural fluid seems to have been secondary to the process below the diaphragm.

What about the genitourinary system? He had a large, probably benign prostate that had nothing to do with the major part of the picture. He had a normal nonprotein nitrogen, and a quite normal urine considering the extent of the illness. There was no real evidence for serious disease in either the kidneys or the prostate. That leaves the upper abdominal and retroperitoneal organs to be considered. We know that he probably had a duodenal ulcer that had been active for many years off and on; however, there is no evidence in the x-ray films of active disease at the time of admission. I do not think he would have had a perforation of a duodenal ulcer that was partially walled off without more evidence in the x-ray films. There was no evidence of a primary carcinoma of the stomach in spite of the fact that the Papanicolaou smear was reported positive. That test is not sufficiently diagnostic to enable me to consider carcinoma very seriously.

The patient had disease in the liver. He had a history of an alcoholic intake and an enlarged liver on x-ray examination. The cephalin-flocculation abnormality was borderline, and the prothrombin time gradually became longer but not strikingly so. It is possible that he had a mild cirrhosis; it was not particularly striking when the peritoneoscopist looked at the left lobe of the liver. It does not seem likely that this was the major cause of the illness.

Was the gall bladder the site of the process? A perforated gall bladder could explain the presence of the bile in the abdominal fluid. There was no evidence of gall-bladder disease and no evidence of any gallstones — the patient's history was more suggestive to his previous physicians of duodenal ulcer than of gallstones. I cannot either exclude or make a definite diagnosis of gall-bladder disease.

Despite the fact that he had diarrhea early in the course of the illness, the colon is excluded by the apparently normal colonic function, the negative stool guaiac reaction and the barium-enema examination that was negative except for extrinsic displacement of the colon.

That leaves the pancreas, which is a likely possibility. He had a high amylase, but a high amylase is not diagnostic of acute pancreatitis. A process involving the region of the pancreas might well have elevated the amylase; we have seen a high amylase with perforated duodenal ulcers and other conditions. Pancreatitis would explain the fluid in the abdomen and the fact that the abdominal fluid was bile stained, that it contained some blood and possibly that it contained some albumin; it would also explain the fever and might explain the peritoneal nodules, which may have represented fat necrosis. Since there was no widening of the duodenal loop, I should have to say that the inflammation was in the body or in the tail of the pancreas. Later, the mass was thought to be movable with respiration; if that was true, it is an argument against pancreatitis causing a large mass of necrosis in the tail or body. Another finding that I have difficulty in explaining is the progressive bleeding into the abdomen from acute pancreatitis alone. We have seen patients with acute pancreatitis that has smoldered for a long long time, but eventually they recover or they die as the result of difficulty with nutrition and with sepsis. I do not recall one that continued to bleed into the abdominal cavity unless there was erosion of a major vessel by the necrosis in or about the pancreas. However, I certainly think an acute pancreatitis with necrosis of the body and tail is a diagnosis that cannot be excluded. The evidence from peritoneoscopy is that the bleeding was of diffuse origin, in spite of the fact that the prothrombin time was only slightly prolonged.

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Carcinoma of the pancreas is also a possibility; yet there was no positive evidence for it. It would have been helpful if the biopsy of the nodule had shown carcinoma; I am assuming that it was taken through the nodule and not in an inflammatory area adjacent to the nodule. Almost all that I have said about acute pancreatitis can be said about carcinoma of the pancreas, which would also explain the continued bleeding. However, I cannot make a positive diagnosis of carcinoma of the pancreas.

The last diagnosis I shall consider is disease of the retroperitoneal lymph nodes, specifically lymphoma. There was no evidence of any other palpable lymph nodes or of an enlarged spleen, unless the mass that appeared in the left upper quadrant toward the end of life was an enlarged spleen, but that does not necessarily exclude intra-abdominal lymphoma. It would explain the progressive course, the fluid in the abdomen, possibly the continuous bleeding and even the anemia and leukocytosis. The temperature would be explained on this basis. May I see the temperature chart?

DR. EDGAR B. TAFT: Here it is.

DR. RAKER: The temperature chart does not show periodicity so that does not help me. I have to select the most likely diagnosis out of those I have mentioned, and I think I shall stick with retroperitoneal lymphoma unless Dr. Schulz can show me something in the x-ray films.

DR. MILFORD D. SCHULZ: I do not believe that the x-ray films contribute much. The abdomen is distended; there is a small mass apparently displacing the colon as described in the protocol. The right leaf of the diaphragm is elevated; there is some fluid in the pleural cavity but not much. I do not believe I can really outline the hepatic and splenic shadows. The stomach looks quite normal, and I should not be too concerned about the duodenum.

DR. RAKER: I am a little more impressed by the displacement of the hepatic flexure than I expected to be.

DR. SCHULZ: Here is a queer thing; on two examinations made on two different days, one can see an area of increased density within a greater area of increased density due to the abdominal fluid that almost looks like a dense, shrunken liver (Fig. 1). If this is a dense, shrunken liver, one wonders if the patient had ever had Thorotrast.

DR. RAKER: Is it a walled-off abscess?

DR. SCHULZ: That should have the same density as the fluid around it. I believe we have seen such small dense livers produced by abnormal iron deposits within the liver substance.

DR. RAKER: You would regard the duodenal cap as quite normal?

DR. SCHULZ: It shows deformity. I suppose it was a fluoroscopic observation.

DR. RAKER: I am impressed with the downward displacement of the hepatic flexure. On that and the elevation of the right leaf of the diaphragm — I did not expect to see so much evidence of localization in the right upper quadrant — I shall vote for disease of the gall-bladder area, possibly a perforated, partially walled-off gall bladder rather than a lymphoma.

DR. PERRY J. CULVER: Dr. Raker is correct about our trying to diagnose this case up to the end. The question arose whether or not the nodules on the peritoneal surface could be pancreatitis. I should like to have Dr. Benedict tell us what he thought about it.

DR. EDWARD B. BENEDICT: Although these small tubercle-like nodules on the peritoneal surface were not typical of anything, I leaned toward carcinomatosis as their cause. The other likely possibility is tuberculous peritonitis, which often cannot be told from carcinomatosis except histologically. I recall that Dr. Tracy B. Mallory told me the pathologist frequently could not tell tuberculous peritonitis from carcinomatosis until after microscopical sections were examined. We have seen fat necrosis from pancreatitis at peritoneoscopy, but I thought it was not fat necrosis in this case. When the biopsy was reported negative for carcinoma and for tuberculosis, that put the process into the inflammatory class. The accuracy of peritoneoscopic biopsy is high, and I believe we took the biopsy from the right location.

DR. TAFT: I should like to ask what you thought about the positive gastric smear.

DR. RAKER: I discounted that because it was not of sufficient diagnostic value to warrant the making of the diagnosis of carcinoma of the stomach on that basis alone in the presence of a normal-looking x-ray film of the stomach.

CLINICAL DIAGNOSES

Carcinomatosis.
?Carcinoma of stomach.
?Tuberculous peritonitis.
Hepatorenal failure.
Pulmonary congestion.

DR. RAKER'S DIAGNOSIS

Cholecystitis, with perforation and right-upper-quadrant abscess formation.

ANATOMICAL DIAGNOSES

Pancreatitis, chronic, with fibrosis and abscess formation.
Peritonitis, diffuse, with abscess in omental bursa.
Hemochromatosis, with involvement of liver, spleen and pancreas.
Pulmonary abscess.
Phlebothrombosis, right femoral vein.
Pulmonary embolism, small.
Coronary atherosclerosis, moderate.

Pathological Discussion

Dr. Taft: When the abdomen was opened, there was approximately 700 cc. of bloody ascitic fluid and, as Dr. Benedict described in his notes, diffuse involvement of the peritoneal surface with fibrinous and sometimes bloody exudate. There was a moderate amount of clotted blood in the pelvis. An abscess cavity, illustrated in this drawing (Fig. 2) by Dr. Carlos Tejada, who performed the autopsy, lay between the stomach, the transverse colon, the pancreas and the mesocolon. This had ruptured into the general peritoneal cavity through the mesocolon. On further dissection three additional abscesses were found: one moderately large, along toward the tail of the pancreas which communicated with this larger abscess in the lesser peritoneal cavity, one about in the middle of the pancreas and a smaller one in the head of the pancreas. Microscopically, there was a marked chronic pancreatitis, as well as these acute abscesses, and considerable fibrosis; so that these abscesses undoubtedly represented an exacerbation of a chronic process. The biliary duct was slightly dilated, but I think that was due to the abscess in the head of the pancreas, not to intrinsic disease, although it is hard to determine that. The gall bladder was not abnormal.

There were some incidental findings: a small abscess in the lung, a phlebothrombosis of the right leg and a small pulmonary infarct. The liver, in spite of these shadows in the films and the fact that it was palpable, was not enlarged. In the kidney there was a moderate amount of healed pyelonephritis, which probably was not significant. There was moderate coronary atherosclerosis.

Surprisingly enough, and I must say I think we should bow to Dr. Schulz, was the fact that this patient had hemochromatosis. It was not recognized even pathologically until we saw the microscopical sections. It was not marked, but there was considerable deposition of hemosiderin in the liver, spleen and pancreas, with a small amount of fibrosis in the liver.

The question arises whether the chronic pancreatitis in this patient was at least in part the result of pancreatic fibrosis associated with hemochromatosis. As far as I can find in the literature, acute abdominal pain is frequently the presenting symptom in patients with hemochromatosis. Some patients have died during the course of this first attack of pain, which is frequently accompanied by shock; all the cases reported have shown no anatomic reason for death. It is interesting to speculate in the case under discussion whether the mild and perhaps completely incidental hemochromatosis had any relation to the final illness.

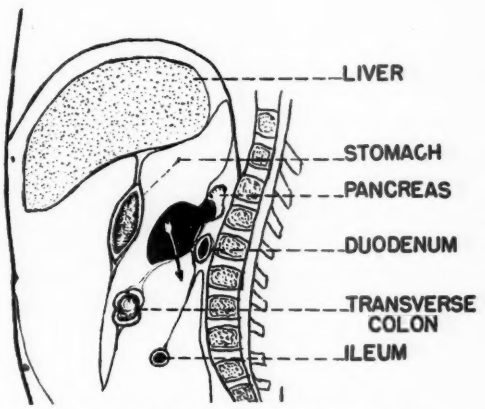

Figure 2. *Drawing, Showing Abscess Cavity. The solid black area represents the abscess. The arrow indicates the site of the rupture into the peritoneal cavity.*

A Physician: How large was the liver?

Dr. Taft: It weighed 1450 gm.

Dr. Culver: Do you think there was enough bleeding into the abdominal cavity to explain the death?

Dr. Taft: The peritonitis was adequate to explain death without intra-abdominal bleeding.

A Physician: Was there diabetes?

Dr. Taft: There was no glycosuria; a blood-sugar determination was not done.

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CORN AND WINE

THANKSGIVING, among all the nation's holidays, is the one on which a fast day, by the simple addition of a vowel, has been changed into a day of feasting. Recognized and appropriately celebrated throughout America, it seems nevertheless to be a day whose observance is peculiarly identified with New England, at least in the minds of New Englanders.

Designed and set apart as an occasion on which to give thanks for the bounties of the harvest, it may be considered to express as a triumph over geography (in New England in particular) the ability to produce any crop whatsoever among the granite hills and rock-sown acres of so many sections of this terrain. New Englanders, being a devout breed of men and women, give thanks where thanks are due, for only with divine help could they in certain years produce a crop at all.

But what may be lacking in abundance of produce is made up for by its color and sweetness, as if its roots had tapped through this thin soil the very Rock of Ages, and by the courage and fortitude of those New Englanders who, no doubt lacking the prairie schooners in which to make the voyage, remained as part of the local scene when their uncles and brothers, accompanied by their aunts and sisters-in-law, set out for the winning of the west. Hippocrates once wrote to the effect that where the climate is severe, the people are "hard, stubborn and independent," and he might have added a few words relative to the tillage of a terminal moraine. The very rock foundations of New England, however, give substance to her hills and valleys and form the landscapes on which her fame is partly based.

Thanksgiving, in New England, marks that period of the year when the ultimate transition from flamboyant fall to the bleaker winter months is anticipated. The colors of the autumn are gone, except for the subdued tones of those oaks that still retain their foliage; most of the deciduous trees stand bare. It represents the acme of the season characterized by piles of yellow pumpkins and of squash, and of golden corn — corn reminiscent, this year, not so much of that legendary Thanksgiving dinner of the Plymouth pilgrims, where only a few kernels were available for each still grateful person, and belts were tightened, as of a political campaign so recently survived in which the same golden medium, renowned for its quality of volumetric expansion, was dished out in abundance, and the exact location of the belt became in doubt, let the blows fall where they might. One is reminded also that in New England, regardless of the customs encountered in the Land of Beulah and elsewhere, corn is accompanied not by the tramplings from any vineyard, but by deep draughts of the product of the local cider presses, in various stages of petrification.

However else it may be taken, this is the season when one remembers that he reaps in fulfillment of

his sowing; that with application and good fortune and guidance beyond the wisdom of man, the harvest is according to the planting.

GEOGRAPHY OF HUNGER

WITH an understanding of science, man is able to measure and predict many features of the future, the seasons, rainfall and the floodtides; the rhythms and toll of disease and starvation; the rise and fall of populations; and the relation of a nation's numbers to sickness, war, water, hunger and harvests. Yet a fruitful application of the scientific method to such social problems is based quite as much on a consistent use of logic as on science. Thus it is disheartening to see such a distinguished officer of the United Nations as the chairman of the Executive Council of its Food and Agriculture Organization, Dr. Josué de Castro, suddenly cast adrift from logic at a crucial moment in his approach to the joint problem of world population and chronic hunger of the masses.

His book* is advanced as a demonstration that "the widespread starvation in great areas of the world is not the result of overpopulation" but its cause. Extolled on its cover jacket as supported "with astonishing and sometimes terrifying facts and figures," the book contains a few small tables tucked here and there among its more than 300 pages, gives a reasonably complete and popularized review of laboratory knowledge of nutrition and an interesting presentation of man-made factors resulting in chronic hunger consequent to artificial sugar-cane or tobacco "monocultures." It does perform a service in focusing world attention on social problems of nutrition that are too often shrugged off as admitting of no solution.

The lesser issues are so well handled that the reader is wholly unprepared to find that the main thesis of the book, "my theory that specific hunger is the cause of overpopulation," is oversimplified to an absurd degree. The rigid rules of science that were used in Dr. de Castro's considerations of vitamin, protein and calcium deficiencies are replaced by dogma when his theory is considered. Isolated facts and figures are pulled out of their context of natural history with much skill to support the preconceived conclusion. Although described by the publishers as a book "that may well change world thinking on one of mankind's most crucial problems," the treatise avoids at critical junctures the careful, dispassionate ways of science, choosing instead the dialectic methods of the debate, and even the emotional persuasiveness of demagoguery.

Approaching the many-sided problem of world overpopulation in terms of a single simple cause, hunger, Dr. de Castro virtually ignores the other forces that combine to determine a people's numbers — notably communicable and noncommunicable disease, accidental or deliberate violence and purposeful conduct or measures undertaken to limit progeny. He embraces his subject with a rally-cry, a quotation from Romain Rolland inscribed on the fly-leaf: "The heroic lie is a cowardice. There is only one heroism in the world; to see the world as it is and to love it." There is only one point of view that is heroic and that champions the truth — Dr. de Castro's. Those who do not agree with him are in the position of being a group of blackguards who "would deliberately withhold the benefits of modern technology from over-crowded areas of the world to stifle them to death." Although he mentions specific problems of "demographic metabolism," whatever that is, it is with a fine disregard for confines of time and space, the natural increase of a country's population, the accomplishments of therapeutic and preventive medicine and factors of emigration that have eased the problem in the historic past. He refers to over 300 works on nutrition and demography, — Boudreau and Stare, for example, — but without regard for conflicting facts and interpretations advanced by such investigators.

Pronouncement follows pronouncement, dissident thinkers being banished from consideration as if to an intellectual Siberia where their queries are not heard and do not have to be answered. Thus the statement that "history itself has completely disproved the predictions of Malthus" takes care of the gloomy curate under a tiny section called "The Malthusian Scarecrow." To be sure, the Malthusian cliché, "population increases in geometrical, land in arithmetical ratio," can be branded as disproved by history in the sense that an interminable debate

*de Castro, J. *The Geography of Hunger.* 352 pp. Boston: Little, Brown & Company, 1952.

arises when it comes to defining what is meant by land increase. No such haziness is evident when the problem is presented in terms of island populations of Great Britain and Eire, Puerto Rico, the Philippines or the Continental island of Italy. The Neo-Malthusian principle is clear enough: that man increases his numbers in geometrical ratios to potentially infinite numbers; and that the land areas of islands (and ultimately continents) are finite, no matter how much sustenance is squeezed out of them. The population of Great Britain is well fed, as far as essential nutrients go, but for all that was rationed to less than twenty cents worth of beef per person per week in the long postwar period. Dr. de Castro's solution for the world problem is easy — all that is necessary is to feed people: "The truth is that soil erosion and over-population can at most be regarded as capable of causing hunger in future epochs, but never in our era." Somewhere, somehow, an ecologic equilibrium must be brought about if man does not wish to share the fate of bacteria in a test tube, weeds in his garden or rabbits in Australia. No responsible scientist who contemplates the potential cruelty of nature advocates genocide by stifling to death seething humanity in overcrowded areas; the author whips a straw man with one hand while he proffers a sugar-coated pill with the other.

The most curious of all unwarranted statements in the book is the pronouncement that since hunger is a spur to sexual activity an abundance of food is the automatic control to population increase. "Cattle raisers have long known that animals which get too fat may become sterile, and that reduced rations will re-establish fertility. . . ." The point is made again for rats and finally for human societies. The fallacy, of course, is that although clear distinction is made between undernutrition and optimum nutrition, obesity is made synonymous with the latter state. From the observation that obesity may cause relative sterility Dr. de Castro infers that optimum nutrition also reduces fertility beyond what would be expected with semistarvation rations. Just as glaring an error in logic is the failure to distinguish between sexual activity, as such, and reproduction in terms of progeny actually born. Completely at odds with the fantastic idea that good nutrition carries in its wake automatic regulation of fertility and fecundity is everyday experience with laboratory animals, clinical experience with the average well fed, healthy American family and the single simple demographic fact that the population increase in the United States alone exceeded all statistical predictions when, despite the war, people were better fed than at any time in their history. The census mushroomed up by 19,000,000 persons within a single decade.

"Hunger is responsible for the overproduction of human beings excessive in number and inferior in quality, who are hurled blindly into the demographic metabolism of the world." This is Dr. de Castro's thesis — stark, magnificent and clothed in the splendid verbiage of science, but without logic. One is reminded of Hans Christian Andersen's tale of the Emperor's new clothes — the Emperor, it was apparent, had nothing on.

MOST RIGHTFUL JUDGES!

Among the Herculean labors that present-day morality must undertake, that of stamping out the hydra-headed monster of medical quackery is not the least. It is therefore encouraging to record the occasional lopping off of a head, particularly if the cauterization of its stump can also be accomplished.

Such a blow was recently administered by a United States Circuit Court of Appeals to the Hoxsey Cancer Clinic of Dallas, Texas. The Hoxsey Clinic pretends to cure cancer by means of black medicine (cascara sagrada, potassium iodide, buckthorn, prickly ash, red-clover blossom, alfalfa, sugar and water) and pink medicine (elixir of lactated pepsin containing potassium iodide).

The Circuit Court reversed the decision of a Texas trial judge that "some it cures, and some it does not cure, and some it relieves somewhat," by pointing out the following important principles based on testimony by cancer experts:

> . . . there is only one reliable and accurate means of determining whether what is thought to be cancer is . . . actually cancer. This requires a . . . microscopic examination of a piece of tissue removed from the . . . diseased region.
>
> . . . the opinion of a layman as to whether he has . . . cancer or . . . whether he has been cured . . . is entitled to little if any weight.

> . . . the aggregate of medical experience and qualified experts recognize in the treatment of internal cancer only the methods of surgery, x-ray, radium and some of the radio-active by-products of atomic bomb production.
>
> . . . Upon such subjects a court should not be so blind and deaf as to fail to see, hear and understand the import and effect of such matters of general public knowledge and acceptance, especially where they are established by the overwhelming weight of disinterested testimony . . . .

An upright court; a learned court!

An injunction was ordered to be issued prohibiting the Hoxsey Clinic from distributing its products in interstate commerce, although under the law the Clinic has the right to petition for review by the United States Supreme Court.

THE CHRISTMAS SEAL AND TUBERCULOSIS CONTROL

EACH year the campaign of the National Tuberculosis Association, which begins with the sale of Christmas Seals in the middle of November, is inaugurated in the light of further progress in control of tuberculosis. The advances made since 1904, when the Association was founded and the first campaign was launched, are impressive: tuberculosis has dropped to sixth place among the leading causes of death, the rate in the United States decreasing from 202 per 100,000 population in 1900 to 20 in 1951.* Phrased in another way, these figures mean that 6,000,000 lives have been saved by the successful discoveries of methods of control and treatment. In recent years chemotherapy and various surgical procedures have constituted the most dramatic of the new technics.

Unfortunately, this noteworthy record does not mean that the public-health and economic problems of transmission, treatment and rehabilitation have been eliminated or that tuberculosis is no longer a major cause of death. It costs the nation approximately 1,000,000 working years annually, and the care of patients, building and maintenance of hospitals and pensions require an expenditure of well over $350,000,000 a year. The disease kills more people than all other infectious diseases combined, accounting for 30,000 deaths in the United States in 1951 and leading all diseases as a cause of death among persons fifteen to thirty-five years of age.

The problem is, in effect, one of extending gains so far made to the point of adequate control and eventual eradication. The National Tuberculosis Association takes up the challenge by means of its program of education, case finding, rehabilitation and medical research, not the least of its activities being an effort to discover the estimated 150,000 unknown cases. Once the unknown cases have come to light, the problem of control will be greatly simplified: the disease is caused by a specific germ, it can frequently be cured, and it can be prevented.

The Christmas Seal is at once a symbol of the remarkable progress already achieved and an earnest of future advances. The donations requested during the campaign appear small in comparison with the present annual cost of care of patients with tuberculosis. A generous response to the appeal means that the three thousand affiliated agencies of the National Tuberculosis Association, which depend entirely on the sale of Christmas Seals for support, will be able to continue their efforts to control a disease that is still a leading killer and a major social and economic problem.

*King, D. S. Tuberculosis. *New Eng. J. Med.* 247:718-725, 1952.

STUDENT PRIZE ESSAY

Fourth-year students are reminded of the 1953 prize-essay competition.

Full details may be found in the issue of October 16.

The following papers are on file, in addition to those already acknowledged: — *Media Sacra; Thermometrical Observations in Missouri; Medical Application of Electricity;* and *Use of the Stethoscope in Midwifery.*

Boston M. & S. J., *November 24, 1852*

MASSACHUSETTS MEDICAL SOCIETY

COLLEGE OF AGRICULTURE AND APPLIED SCIENCE LIBRARY DEC 8 1952 MANHATTAN KANSAS

DEATHS

BEALS — Arthur L. Beals, M.D., of Brockton, died on October 20. He was in his eighty-fourth year.

Dr. Beals received his degree from Columbia University College of Physicians and Surgeons in 1895. He was formerly a member of the staff of Brockton Hospital and school and city physician, and was a fellow of the American Medical Association.

He is survived by two daughters and a sister.

SANGER — Guy E. Sanger, M.D., of Arlington, died on October 14. He was in his seventy-fourth year.

Dr. Sanger received his degree from Harvard Medical School in 1903. He was formerly a member of the staff of Symmes-Arlington Hospital and of the Arlington Board of Health, and was a fellow of the American Medical Association.

He is survived by two sons and four grandchildren.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The December schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

Orthopedic Clinic	Date	Clinic Consultant
Salem	December 1	Paul W. Hugenberger, M.D.
Gardner	December 2	Carter R. Rowe, M.D.
Haverhill	December 3	William T. Green, M.D.
Greenfield	December 4	Charles L. Sturdevant, M.D.
Lynn*	December 8	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Brockton	December 11	George W. Van Gorder, M.D.
Lowell	December 12	Albert H. Brewster, M.D.
Worcester	December 12	John W. O'Meara, M.D.
Springfield	December 16	James D. Fisher, M.D.
Pittsfield	December 17	Edward J. Coughlin, Jr., M.D.
Hyannis	December 18	Paul L. Norton, M.D.
Fall River	December 22	David S. Grice, M.D.

Rheumatic-Fever Clinics	Dates
Fitchburg	December 3, 10, 17, 24, 31
North Reading	December 2, 9, 16, 23, 30

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

APPOINTMENT OF DR. FIUMARA TO TUFTS STAFF

Nicholas J. Fiumara, M.D., M.P.H., has been appointed a lecturer in dermatology and syphilology at Tufts College Medical School.

Dr. Fiumara joined the Massachusetts Department of Public Health in 1941. In 1947, he was appointed director of the Division of Venereal Diseases. He is a consultant in venereal diseases to the United States Public Health Service; since 1946 he has been a civilian consultant in venereal diseases to the Armed Forces Disciplinary Control Board, and he is a lecturer in venereal diseases at Boston University School of Medicine.

Between 1943 and 1946, Dr. Fiumara was on a military leave of absence from the Massachusetts Department of Public Health. On active duty with the Navy, he served first as venereal-disease and communicable-disease control officer for the Caribbean Theater and then as the commanding officer of Epidemiology Unit No. 22.

CORRESPONDENCE

RESTORATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held October 23, 1952, it was voted to restore the registration of Dr. Manford R. Spalding, of East Gardner, Massachusetts, formerly of Worcester, Massachusetts.

Robert C. Cochrane, M.D.
Secretary

State House, Boston

INCIDENCE OF UNKNOWN INTRATHORACIC CANCER

To the Editor: In the editorial comment on the paper by G. Bondi and myself in the October 2 issue of the *Journal* the incidence of unknown intrathoracic cancer found in our series is erroneously indicated as "approximately 1 in 1000 persons studied."

The incidence, as stated in our paper, is approximately 1 in 10,000.

Vera Leites, M.D.

New York City

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held October 23, 1952, it was voted to revoke the registration of Dr. David Ginsburg, 175 State Street, Springfield, Massachusetts.

Robert C. Cochrane, M.D.
Secretary

State House, Boston

DOSAGE OF QUINIDINE

To the Editor: It was only a few years ago that I first learned from a commercial brochure on quinine and its isomer what an uncommonly large dose of quinidine may be required for the effectual treatment of certain cardiac cases — namely, 0.2 gm. (3 gr.) every two hours, night and day till relief or untoward effects ensue, for four days if necessary. Since then, in my own practice, I have so administered it with surprising success after a period of two and a half days or less.

From my observations the efficacy and the safety of such a dosage of quinidine is not generally recognized in the East, where the fear that the drug itself might cause embolism, still lingers. In the less conservative West, on the other hand, large doses prevail.

Gilbert W. Haigh, M.D.

Worcester, Massachusetts

NOTICES

ANNOUNCEMENT

Dr. Joseph A. Lundy announces the removal of his office from 16 Norwich Street to 511–512 Chamber of Commerce Building, 32 Franklin Street, Worcester.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, December 10. The usual clinical activities will be presented during the day in the Auditorium of the Jimmy Fund Building, Binney Street, Boston. The program of the evening meeting, which will be held at Longwood Towers, is as follows:

The Evolution of the Concepts of Infant Feeding. Alton Goldbloom, M.D., physician-in-chief, The Children's Memorial Hospital, Montreal, and professor of pediatrics, McGill University Faculty of Medicine, Montreal.

MASSACHUSETTS HEART ASSOCIATION GRANTS FOR RESEARCH IN CARDIOVASCULAR DISEASES

The Research Allocations Committee of the Massachusetts Heart Association will consider requests from institutions for grants-in-aid from the fund for research in cardiovascular diseases during 1952-1953.

The Committee meets bi-monthly during the year to review applications. To be placed on the agenda of any given meeting, applications should be in the hands of the Committee at least one week in advance of the meeting. Requests received after the deadline will be placed on the agenda of the next following meeting.

All applications should be addressed to Samuel Proger, M.D., chairman, Research Allocations Committee, Massachusetts Heart Association, 650 Beacon Street, Boston. Each application should be accompanied by a note of endorsement from the administrator of the institution in which the research is to be done.

PRIORITIES FOR MASSACHUSETTS PHYSICIANS AND DENTISTS

Massachusetts Special Call No. 8, Priorities I and II Physicians, Priorities I and II Dentists and Priority III Dentists, born in years 1917 through 1929, is as follows (date of induction, November 28, 1952).

No. P–1 physicians: 7
No. P–2 physicians: 7
No. P–1 dentists: 1
No. P–2 dentists: 0
No. P–3 dentists: 2

NEW YORK SOCIETY FOR CIRCULATORY DISEASES

The sixth regular meeting of the New York Society for Circulatory Diseases will be held in Room 440, New York Academy of Medicine, on Tuesday, December 9, at 8:30 p.m., with Simon Dack, M.D., presiding.

PROGRAM

Problems in Exclusion of the Mammalian Heart, with Applications to Cardiovascular Surgery. Lester Blum, M.D., Samuel J. Megibow, M.D., and William M. Nelson, Ph.D.

Resection of the Left Auricular Appendage for Recurrent Arterial Embolization. Robert A. Nabatoff, M.D.

Results of Cardiopericardiopexy for the Treatment of Rheumatic Heart Disease. Aaron N. Gorelik, M.D.

Details of the program may be obtained from the secretary, Gabriel F. Greco, M.D., 114-08 Linden Boulevard, Ozone Park, New York.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The winter meeting of the New England Society of Anesthesiologists will be held at St. Francis Hospital, Hartford, Connecticut, on Friday, February 6, 1953.

PROGRAM

8:00 a.m. to 12:30 p.m. Operating-room schedule, fourth floor.

12:30 to 2:00 p.m. Lunch.

2:00 to 5:00 p.m. McAuliffe Memorial Auditorium.
Transfusion Reactions and Anesthesia.
Dr. Peter Tucci, Department of Anesthesiology, St. Francis Hospital.
Antisepsis of Endotracheal Tubes.
Dr. Wilfrid McDonald, Department of Anesthesiology, St. Francis Hospital.
Evaluation of Succinylcholine Chloride.
Dr. John Pierce, Department of Anesthesiology, St. Francis Hospital.
Clinical Impressions of Hexamathonium Salts.
Dr. Ronald Stevens, Department of Anesthesiology, Hartford Hospital.

6:00 to 7:00 p.m. Dinner. Bond Hotel.

7:30 to 8:00 p.m. Business Meeting. McAuliffe Memorial Auditorium, St. Francis Hospital.

8:00 to 9:00 p.m. Recent Laboratory Studies and Clinical Applications of Cyclopropane Anesthesia. Dr. E. A. Rovenstine, professor of anesthesiology, New York University Medical College, New York City.

SPRINGFIELD HOSPITAL EDUCATIONAL PROGRAM

The educational program of the Springfield Hospital has been prepared for the month of December as follows:

Monday, December 1

6:30 p.m. Diaphragmatic Hernias. Staff Conference Room. Dr. Robert A. Grugan.

Wednesday, December 3

1–2 p.m. Orthopedic Conference, Staff Conference Room.

Friday, December 5

11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.
6:30 p.m. Surgery and Tuberculosis. Staff Conference Room. Dr. Frederick A. Post.

Saturday, December 6

8:30–10:00 a.m. Surgical Service Conference in Classroom, second floor.
10–11 a.m. Grand Surgical Rounds, Staff Conference Room.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds, Staff Conference Room.

Monday, December 8

6:30 p.m. Surgery of the Thyroid Gland. Staff Conference Room. Dr. Arthur E. Gramse.

Wednesday, December 10

1–2 p.m. Pediatric Conference, Staff Conference Room. Dr. H. H. Shuman.

Friday, December 12

11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.
6:30 p.m. Surgery and the Parathyroid Gland. Staff Conference Room. Dr. Arthur E. Gramse.

Saturday, December 13

8:30–10:00 a.m. Surgical Service Conference, Classroom, second floor.
10–11 a.m. Grand Surgical Rounds, Staff Conference Room.
11 a.m. to 12 m. Clinicopathological Conference, Staff Conference Room.

Monday, December 15

6:30 p.m. Interpretation of Scout Film of Abdomen. Staff Conference Room. Dr. Robert A. Grugan.

Tuesday, December 16

8:30 p.m. Guest Speaker Conference, Staff Conference Room. (Speaker and topic to be announced.)

Wednesday, December 17

1–2 p.m. Orthopedic Conference, Staff Conference Room.

Friday, December 19

11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.
6:30 p.m. Precancerous Lesions of the Breast. Staff Conference Room. Dr. Omar T. Pace.

Saturday, December 20

8:30–10:00 a.m. Surgical Service Conference, Classroom, second floor.
10–11 a.m. Grand Surgical Rounds, Staff Conference Room.
11 a.m.–12 m. Combined Medical and Surgical Death Reviews, Staff Conference Room.

Monday, December 22

6:30 p.m. Colonic Lesions. Staff Conference Room. Dr. Robert A. Grugan.

Every Wednesday morning from 11 to 12 a psychosomatic and group psychotherapy conference is held in the Staff Room under the direction of Dr. Calvert Stein.

Every Thursday from 3 to 4 p.m. a pathology conference is held in the Staff Conference Room.

There will be no conference after December 22 for the remainder of the month because of the Christmas holidays.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The eleventh annual meeting of the American Academy of Dermatology and Syphilology will be held in the Palmer House, Chicago, December 6-11.

Principal sessions will be held Monday through Thursday, December 8-11, and special courses in histopathology, mycology, roentgenology and radium, bacteriology of the skin and research methods of dermatology will be held Saturday and Sunday at the college of medicine, University of Illinois, Northwestern University, Billings Hospital and in the Palmer House.

Ninety-two exhibits, including 31 scientific exhibits and 61 technical exhibits, will be held in the hotel. At noon and late afternoon of each day except Thursday, 36 informal discussion groups are scheduled.

NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

The sixteenth annual meeting of the New Orleans Graduate Medical Assembly will be held in New Orleans, March 2-5, with headquarters at the Municipal Auditorium.

Eighteen outstanding guest speakers will participate and their presentations will be of interest to both specialists and general practitioners. In addition, the program will include a symposium on "The Value of Newer Drugs," daily demonstrations of medical and surgical procedures in color television, clinicopathological conferences, medical motion pictures, over 100 technical exhibits and three roundtable luncheons. The Assembly has planned another interesting postclinical tour to follow the 1953 meeting in New Orleans. On Saturday, March 7, a party composed of doctors and their families will leave New York for Europe on the new superliner, *S. S. United States*. The itinerary includes England, France, Switzerland and Italy, and arrangements have been made for medical programs in these countries. The tour ends in Rome, and the group will return to New York on March 31 by Pan American World Airways, President Special.

Details of the New Orleans meeting and the postclinical tour are available at the office of the Assembly, Room 103, 1430 Tulane Avenue, New Orleans 12, Louisiana.

COURSES IN RADIOLOGIC HEALTH PROTECTION

A series of three two-week courses in radiologic health protection, including technical laboratory procedures, will begin on January 19 in Cincinnati, Ohio. Each succeeding two-week course is dependent upon information gained in the preceding weeks. However, the student's previous training and experience may permit him to enter directly the second or third two-week program. Thus, the student, depending upon his particular qualifications and need, may take a two-week, a four-week or a six-week course.

This program, free of tuition, is offered to qualified applicants by the Public Health Service at its Environmental Health Center. Its purpose is to assist health department employees and key personnel in other governmental or private organizations to achieve a working knowledge of the hazards and problems related to use of x-rays, radioelements, neutron fluxes and particle accelerators.

Further information may be obtained from the chief, Radiological Health Training Section, Environmental Health Center, 1014 Broadway, Cincinnati 2, Ohio.

SOCIETY MEETINGS AND CONFERENCES

October 6–December 8 and March 2–May 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

October 7–December 9. Massachusetts Department of Mental Health. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 540, issue of October 2.

November 21. New York Tuberculosis and Health Association. Page 583, issue of October 9.

November 22–29. Springfield Hospital Educational Program. Page 623, issue of October 16.

November 25. Norfolk District Medical Society. Page 583, issue of October 9.

November 26–December 17. Lahey Clinic Lectures. Page 698, issue of October 30.

November 26–April 8. Postgraduate Medical Institute. Page 452, issue of September 18.

December 1–22. Springfield Hospital Educational Program. Page 827.

December 1–March 23. Postgraduate Course in General Medicine. Page 697, issue of October 30.

December 2. Lecture on Cancer Research. Page 697, issue of October 30.

December 5–January 30. Combined Anesthesia Teaching Conferences of Boston. Page 785, issue of November 13.

December 6–11. American Academy of Dermatology and Syphilology. Notice above.

December 9. New York Society for Circulatory Diseases. Page 827.

December 10. New England Pediatric Society. Page 826.

December 10–13. New York State Society of Anesthesiologists. Page 744, issue of November 6.

December 12 and 13. Association for Research in Nervous and Mental Disease. Page 584, issue of October 9.

December 15–17. American Academy of Obstetrics and Gynecology. Page 744, issue of November 6.

January 14, 1953. Essex North District Medical Society. Page 743, issue of November 6.

February 6. New England Society of Anesthesiologists. Page 827.

February 9 and 10. Annual Congress on Medical Education and Licensure. Page 786, issue of November 13.

March 2–5. New Orleans Graduate Medical Assembly. Notice above.

District Medical Societies

ESSEX NORTH

January 14. Pentucket Club. 111 Main Street, Haverhill.

May 13. Andover Country Club, Shawsheen.

MIDDLESEX WEST

December 1–March 23. Postgraduate Course in General Medicine.

NORFOLK

November 25. 8:00 p.m. John Ware Hall, Boston Medical Library.

January 27.

February 24.

March 24.

Calendar of Boston District for the Week Beginning Thursday, November 27

Friday, November 28

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.

10:30 a.m.–1:30 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.

11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*2:30–3:30 p.m. Pulmonary Conference. Drs. Kane, Etsten and others. Stearns Auditorium, New England Center Hospital.

*4:00–6:00 p.m. X-Ray Conference. Dr. Sosman. Stearns Auditorium, New England Center Hospital.

4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

*7:00–9:00 p.m. Combined Anesthesia Teaching Conferences of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

Saturday, November 29

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

Monday, December 1

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

12:00 m. Clinicopathological Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*12:00 m.–1:00 p.m. Hematology Conference. Dr. Dameshek. Stearns Auditorium, New England Center Hospital.

*12:15 to 1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.

*7:00–9:00 p.m. Anesthesia Te hing Conference. Stearns Auditorium, New England Center Hospital.

Tuesday, December 2

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.